FORMULATION AND EVALUATION OF FLOATING TABLETS USING ALFUZOSIN HYDROCHLORIDE AS A MODEL DRUG

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IN

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Submitted by

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CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF FLOATING TABLETS USING ALFUZOSIN HYDROCHLORIDE AS A MODEL DRUG**" submitted by **R.JENISH (26107709)** in partial fulfillment of the degree of Master of Pharmacy in Pharmaceutics of The TamilNadu Dr.M.G.R Medical University, Chennai at Annai Veilankanni's Pharmacy College, Chennai- 600 015 is the Bonafide work carried out by his/her under my guidance and supervision during the academic year 2011-2012. The dissertation or any part of this has not been submitted elsewhere for any other degree.

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Richer Healthcare

To Whom So Ever It May Concern

This is a bonafide dissertation work entitled "**Formulation and Evaluation of Floating Tablets using Alfusozin Hydrochloride as a Model Drug**" Which has been carried out by **Mr.Jenish** from Annai Veilankanni's College of Pharmacy, affiliated to The Tamil Nadu Dr.M.G.R Medical University-Chennai, in partial fulfillment of the requirement for the award of the degree of Master of Pharmacy in Pharmaceutics. This thesis work was carried out at "Richer Health Care Pvt Ltd-Hyderabad, under my supervision and guidance during the academic year 2011-2012.

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DECLARATION

I hereby declare that the dissertation work entitled "**FORMULATION AND EVALUATION OF FLOATING TABLETS USING ALFUZOSIN HYDROCHLORIDE AS A MODEL DRUG** " is based on the original work carried out by me in Annai Veilankanni's Pharmacy College, Saidapet, Chennai and Formulation R&D, Richer Pharmaceutics India Pvt Ltd., Hyderabad under the guidance of **Ms.** R. **Devi** and for submission to The Tamilnadu Dr.M.G.R University in the partial fulfillment of the requirement for the award of degree Master of Pharmacy in Pharmaceutics. The work is original and has not been submitted in part or full for any other diploma or degree of this or any other university. The information furnished in this dissertation is genuine to the best of my knowledge and belief.

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ABBREVIATION	
e.g.	Example
i.e.	That is
%	Percentage
Kg	Kilogram
gm	gram
mg	Milligram
µg	Microgram
ml	Millilitre
cm	Centimetre
mm	millimetre
nm	nanometre
W/w	Weight by weight
V/v	Volume by volume
avg	Average
hrs	Hours
pH	Hydrogen ion concentration
°C	Degree centigrade
RH	Relative Humidity
HCL	Hydrochloric acid
RPM	Revolution per minute
Abs	Absorbance
Conc.	Concentration
Fig	Figure
UV- VIS	Ultra violet and visible spectroscopy
FTIR	Fourier Transform Infra Red spectroscopy
C.I	Compressibility Index
CR	Cumulative Release
GRDDS	Gastro Retentive Drug Delivery System
OCDD	osmotic controlled drug delivery
DSP	Dicalcium phosphate
PEG	poly ethylene glycol

INTRODUCTION

Oral administration is the most convenient and preferred means of any drug delivery to the systematic circulation. Oral controlled release drug delivery have recently been of increasing interest in pharmaceutical field to achieve improved therapeutic advantages, such as ease of dosing administration, patient compliance and flexibility in formulation. This route has high patient acceptability, primarily due to ease of administration. Over the years, oral dosage forms have become increasingly sophisticated with major role being played by 0control release drug delivery system (CRDDS). CRDDS release drug at a predetermined rate, as determined by drug's pharmacokinetics and desired therapeutic concentration. This help in achieving predictable drug plasma concentration required for therapeutic effect. The successful functioning of an oral CRDDS is determined by-

1. Physicochemical properties of the drug molecule like, the aquous solubility, intestinal permeability, pH- solubility profile, etc.
2. Pharmacokinetic profile of the drug.
3. The interaction of these properties with the anatomy and physiology of the GI tract. One such requisite for successful performance of oral CRDDS is that the drug should have the good absorption throughout the GI tract, preferably by passive diffusion.

Drugs that are easily absorbed from gastrointestinal tract (GIT) and have short half- lives are eliminated quickly from the systemic circulation. Frequent dosing of these drugs is required to achieve suitable therapeutic activity. To avoid this limitation, the development of oral sustained-controlled release formulations is an attempt to release the drug slowly into the gastrointestinal tract (GIT) and maintain an effective drug concentration in the systemic circulation for a long time (Ichikawa M *et al*, 1991). After oral administration, such a drug delivery would be retained in the stomach and release the drug in a controlled manner, so that the drug could be supplied continuously to its absorption sites in the gastrointestinal tract (GIT) (Streubel A *et al*, 2006). These drug delivery systems suffer from mainly two adversities: the short gastric retention time (GRT) and unpredictable short gastric emptying time (GET), which can result in incomplete drug release from the dosage form in the absorption zone (stomach or upper part of small intestine) leading to diminished efficacy of administered dose (Iannucelli V,

et al,1998) . To formulate a site-specific orally administered controlled release dosage form, it is desirable to achieve a prolong gastric residence time by the drug delivery. Prolonged gastric retention improves bioavailability, increases the duration of drug release, reduces drug waste, and improves the drug solubility that are less soluble in a high pH environment (Garg R, *et al*, 2008). Also prolonged gastric retention time (GRT) in the stomach could be advantageous for local action in the upper part of the small intestine e.g. treatment of peptic ulcer, etc. Gastroretentive drug delivery is an approach to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal tract (GIT) for local or systemic effects. Gastroretentive dosage forms can remain in the gastric region for long periods and hence significantly prolong the gastric retention time (GRT) of drugs (Moes AJ *et al*, 1993). Over the last few decades, several gastroretentive drug delivery approaches being designed and developed, including: high density (sinking) systems that is retained in the bottom of the stomach (Rouge N,et al,.1998), low density (floating) systems that causes buoyancy in gastric fluid (Goole J,et al,. 2007) mucooadhesive systems that causes bioadhesion to stomach mucosa , unfoldable, extendible, or swellable systems which limits emptying of the dosage forms through the pyloric sphincter of stomach, super porous hydrogel systems , magnetic systems etc. (Fujimori J,et al,.1994). These efforts resulted in GRDFs that were designed, in large part, based on the following approaches.

(a) Low density form of the DF that causes buoyancy in gastric fluid

(b) High density DF that is retained in the bottom of the stomach

(c) Bioadhesion to stomach mucosa

(d) Slowed motility of the gastrointestinal tract by concomitant administration of drugs or Pharmaceutical excipients

(e) Expansion by swelling or unfolding to a large size which limits emptying of the DF through the pyloric sphincter.

BASIC GASTROINTESTINALTRACT PHYSIOLOGY

It is well recognized that the stomach may be used as a 'depot' for sustained-release (SR) dosage forms, both in human and veterinary applications. The stomach is anatomically divided into three parts: that occur fundus, body, and antrum (or pylorus). The proximal stomach, made up of the fundus and body regions, serves as a reservoir for ingested materials while the distal region (antrum) is the major site of mixing motions, acting as a pump to accomplish gastric emptying (Wilson CG, *et al*, 1998). Gastric emptying occurs during fasting as well as fed states. The pattern of motility is however distinct in the 2 states. During the fasting state an interdigestive series of electrical events take place, which cycle both through stomach and intestine every 2 to 3 hours. This is called the interdigestive myloelectric cycle or migrating myloelectric cycle (MMC), which is further divided into following 4 phases as described by Wilson and Washington (Desai S. A 1984).

1. Phase I (basal phase) lasts from 40 to 60 minutes with rare contractions.
2. Phase II (preburst phase) lasts for 40 to 60 minutes with intermittent action potential and contractions. As the phase progresses the intensity and frequency also increases gradually.
3. Phase III (burst phase) lasts for 4 to 6 minutes. It includes intense and regular contractions for short period. It is due to this wave that all the undigested material is swept out of the stomach down to the small intestine. It is also known as the housekeeper wave.
4. Phase IV lasts for 0 to 5 minutes and occurs between phases III and I of 2 consecutive cycles.

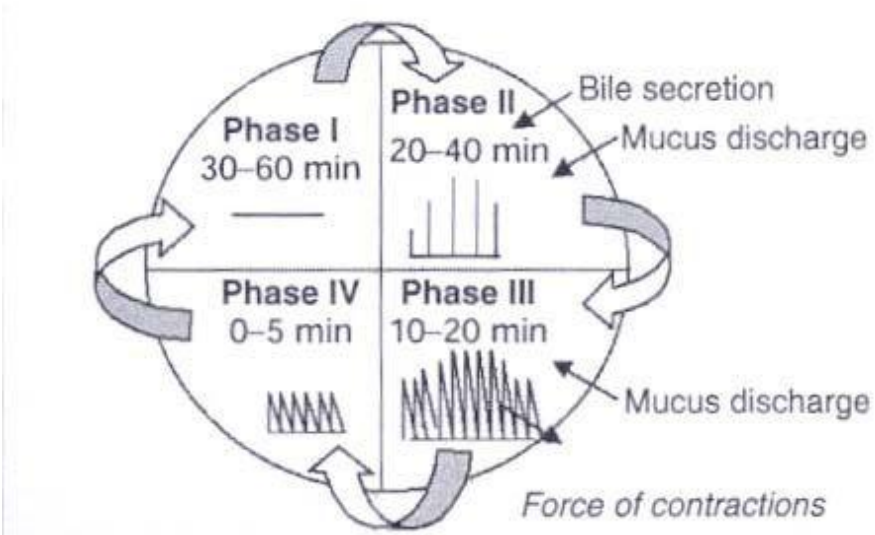


Fig.1 Motility pattern in GIT

After the ingestion of a mixed meal, the pattern of contractions changes from fasted to that of fed state (Edith Madithowitz *et al*, 1999). This is also known as digestive motility pattern and comprises continuous contractions as in phase II of fasted state. These contractions result in reducing the size of food particles (to less than 1 mm), which are propelled toward the pylorus in a suspension form. During the fed state onset of MMC is delayed resulting in slowdown of gastric emptying rate (Asane GS. et al 2007).

SUITABLE DRUG CANDIDATES FOR GASTRORETENTION

In general, appropriate candidates for GRDDS are molecules that have poor colonic absorption but are characterized by better absorption properties at the upper parts of the GIT:

1. Narrow absorption window in GI tract,e.g., riboflavin and levodopa.
2.Primarily absorbed from stomach and upper part of GItract, e.g., calcium supplements,chlordiazepoxideand cinnarazine.
3. Drugs that act locally in the stomach, e.g., antacids and misoprostol.
4. Drugs that degrade in the colon, e.g., ranitidine HCl and metronidazole.
5. Drugs that disturb normal colonic bacteria, e.g., amoxicillin trihydrate.

DRUGS THOSE ARE UNSUITABLE FOR GASTRORETENTIVE DRUG DELIVERY SYSTEMS

1) Drugs that have very limited acid solubility e.g.phenytoin etc.
2) Drugs that suffer instability in the gastric environment e.g. erythromycin etc.
3) Drugs intended for selective release in the colon e.g. 5- amino salicylic acid and corticosteroids etc.

PHYSIOLOGICAL FACTORS CONTROLLING GASTRIC RETENTION OF DOSAGE FORMS

The gastric retention time (GRT) of dosage forms is controlled by several factors such as density and size of the dosage form, food intake, nature of the food, posture, age, sex, sleep and disease state of the individual (e.g., gastrointestinal diseases and diabetes) and administration of drugs such as prokinetic agents (cisapride and metoclopramide).

1. Density of dosage form

Dosage forms having a density lower than that of gastric fluid experience floating behavior and hence gastric retention Baumgartner S et. Al 2000). A density of <1.0 gm/cm3 is required to exhibit floating property. However, the floating tendency of the dosage form usually decreases as a function of time, as the dosage form gets immersed into the fluid, as a result of the development of hydrodynamic equilibrium (Timmermans ,*et al*, 1990).

2. Size of dosage form

The size of the dosage form is another factor that influences gastric retention. The mean gastric residence times of non-floating dosage forms are highly variable and greatly dependent on their size, which may be small, medium, and large units(Taisei Mushiroda *et al*,2000). In fed conditions, the smaller units get emptied from the stomach during the digestive phase and the larger units during the housekeeping waves. In most cases, the larger the size of the dosage form, the greater will be the gastric retention time because the larger size would not allow the dosage form to quickly pass through the pyloric antrum into the intestine. Thus the size of the dosage form appears to be an important factor affecting gastric retention (El-Kamel AH,et al,2002).

3. Food intake and nature of food

Food intake, the nature of the food, caloric content, and frequency of feeding have a profound effect on the gastric retention of dosage forms. The presence or absence of food in the stomach influences the GRT of the dosage form. Usually, the presence of food increases the GRT of the dosage form and increases drug absorption by allowing it to stay at the absorption site for a longer time. The above results are supported by the experiments of Whitehead et al which show an increase in the relative heights of the floating units after meal consumption. Food habits affect the GRT in the following ways:- Fed or unfed state – under fasting conditions, the GI motility is characterized by periods of strong motor activity or the migrating myoelectric complex (MMC) that occurs every 1.5 to 2 hours. The MMC sweeps undigested material from the stomach and, if the timing of administration of the formulation coincides with that of the

MMC, the GRT of the unit can be expected to be very short. However, in the fed state, MMC is delayed and GRT is considerably longer. It was concluded that as meals were given at the time when the previous digestive phase had not completed, the floating form buoyant in the stomach could retain its position for another digestive phase as it was carried by the peristaltic waves in the upper part of the stomach. Nature of meal – feeding of indigestible polymers or fatty acid salts can change the motility pattern of the stomach to a fed state, thus decreasing the gastric emptying rate and prolonging drug release.Caloric content – GRT can be increased by four to 10 hours with a meal that is high in proteins and fats. Frequency of feed – the GRT can increase by over 400 minutes when successive meals are given compared with a single meal due to the low frequency of MMC.(Whitehead L,at el.,1998).

4. Effect of gender, posture and age

A study by Mojaverian et al15 found that females showed comparatively shorter mean ambulatory GRT than males, and the gastric emptying in women was slower than in men. The authors also studied the effect of posture on GRT, and found no significant difference in the mean GRT for individuals in upright, ambulatory and supine state. On the other hand, in a comparative study in humans by Gansbeke et al, the floating and non- floating systems behaved differently. In the upright position, the floating systems floated to the top of the gastric contents and remained for a longer time, showing prolonged GRT. But the non-floating units settled to the lower part of the stomach and underwent faster emptying as a result of peristaltic contractions, and the floating units remained away from the pylorus. However, in supine position, the floating units are emptied faster than non-floating units of similar size (Gansbeke BV,et al,. 1991).(Mojaverian P *et al*, 1988). Effect of buoyancy--On comparison of floating and nonfloating dosage units, it was concluded that regardless of their sizes the floating dosage units remained buoyant on the gastric contents throughout their residence in the gastrointestinal tract, while the non-floating dosage units sank and remained in the lower part of the stomach. Floating units away from the gastro- duodenal junction were protected from the peristaltic waves during digestive phase while the nonfloating forms stayed close to the pylorus and were subjected to propelling and retropelling waves of the digestive phase.(Timmermans J,*et al*,1994).

TYPES OF GASTRORETENTIVE DOSAGE FORM

1. FLOATING SYSTEM - Floating drug delivery systems (FDDS) have a bulk density less than gastric fluids and soremain buoyant in the stomach without affecting gastric emptying rate for a prolonged period of time. While the system is floating on the gastric contents, the drug is released slowly at the desired rate from the system (Taisei Mushiroda et. al., 2000). After release of drug, the residual system is emptied from the stomach. This results in an increased GRT and a better control of the fluctuations in plasma drug concentration. FDDS can be divided into non-effervescent and effervescent system.

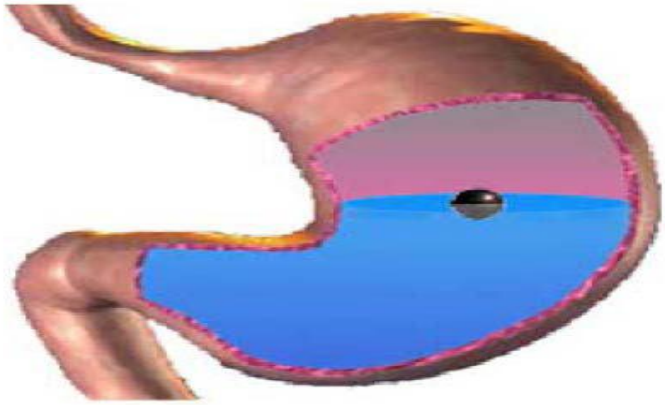


Fig.2 Floating System

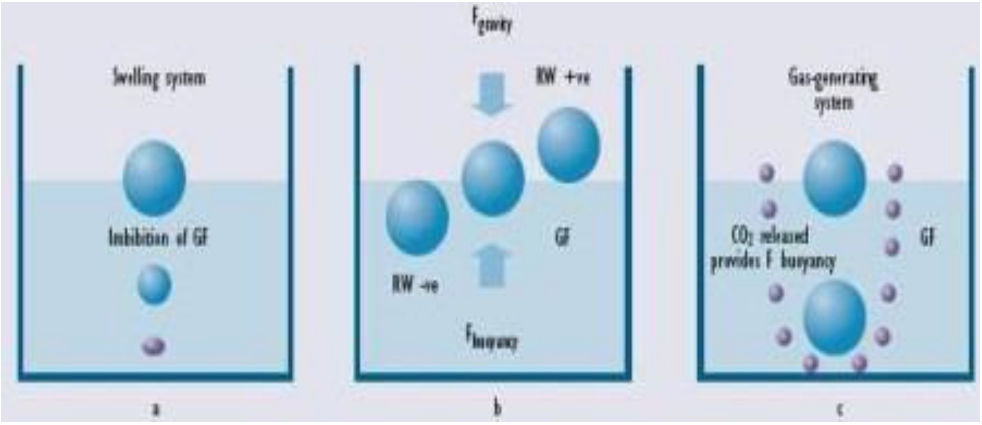


Fig. 1:3 The mechanism of floating systems

A. NON EFFERVESCENT SYSTEMS-

This type of system, after swallowing, swells unrestrained via imbibition of gastric fluid to an extent that it prevents their exit from the stomach.One of the formulation methods of such dosage forms involves the mixing of the drug with a gel, which swells in contact with gastric fluid after oral administration and maintains a relative integrity of shape and a bulk density of less than one within the outer gelatinous barrier (Hilton AK,*et al*, 1992). The air trapped by the swollen polymer confers buoyancy to these dosage forms. Excipients used most commonly in these systems include hydroxypropylmethylcellulose(HPMC), polyacrylate polymers, polyvinyl acetate, Carbopol, agar, sodium alginate, calcium chloride, polyethylene oxide and polycarbonates. This system can be further divided into four sub- types:

a. Colloidal gel barrier system- Sheth and Tossounian first designated this 'hydrodynamically balanced system's. Such a system contains drug with gel-forming hydrocolloids meant to remain buoyant on the stomach content. This prolongs GRT and maximizes the amount of drug that reaches its absorbtion sites in the solution form for ready absorption. This system incorporates a high level of one or more gel-forming highly soluble cellulose type hydrocolloid, e.g., hydroxypropyl cellulose, hydoxyethyl cellulose, hydroxypropyl methyl cellulose (HPMC), polysacharides and matrix-forming polymer such as polycarbophil, polyacrylate and polystyrene. On coming in contact with gastric fluid, the htdrocolloid in the system hydrates and forms a colloid gel barrier around its surface (Seth PR,et al,.1984).

b. Microporous compartment system- This technology is based on the encapsulation of a drug reservoir inside a microporous compartment with pores along its top and bottom walls. The peripheral walls of the drug reservoir compartment are completely sealed to prevent any direct contact of gastric surface with the undissolved drug. In the stomach, the floatation chamber containing entrapped air causes the delivery system to float over the gastric content. Gastric fluid enters through the aperture, dissolves the drug and carries the dissolved drug for continuous transport across the intestine for absorption. (Harrigan RM *et al*,1977).

c. Alginate beads - Multi-unit floating dosage forms have been developed from freeze- dried calcium alginate. Spherical beads of approximately 2.5 mm in diameter can be prepared by dropping sodium alginate solution into aqueous solution of calcium chloride, causing the precipitation of calcium alginate. The beads are then separated, snap-frozen in liquid nitrogen, and freeze-dried at -40ºC for 24 hours, leading to the formation of a porous system, which can maintain a floating force for over 12 hours. These floating beads gave a prolonged residence time of more than 5.5 hours.(Whitehead L,*et al*,1996).

d. Hollow microspheres (microballoons) -

Hollow microspheres loaded with drug in their outer polymer shelf were prepared by a novel emulsion solvent diffusion method22. The ethanol/dichloromethane solution of the drug and an enteric acrylic polymer was poured into an agitated solution of Poly Vinyl Alcohol (PVA) that was thermally controlled at 40ºC. The gas phase is generated in the dispersed polymer droplet by the evaporation of dichloromethane formed and internal cavity in the microsphere of the polymer with drug. The microballoon floated continuously over the surface of an acidic dissolution media containing surfactant for more than 12 h.

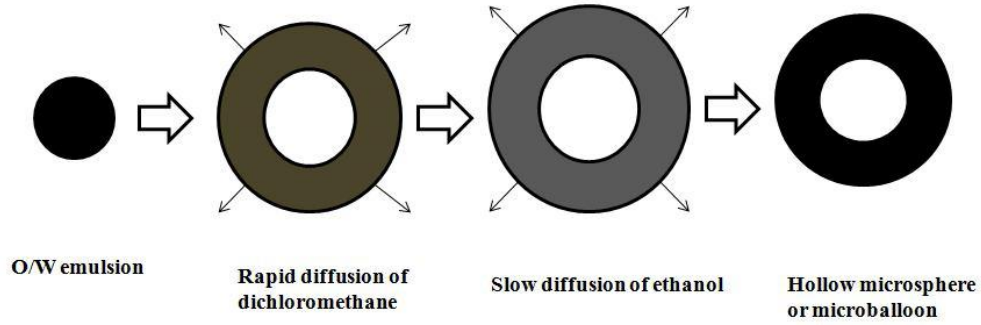


Fig.4: Hollow microspheres

B.EFFERVESCENT SYSTEMS- These buoyant systems utilize matrices prepared with swellable polymers such as methocel, polysaccharides (e.g., chitosan), effervescent components (e.g., sodium bicarbonate, citric acid or tartaric acid). The system is so prepared that upon arrival in the stomach, carbon dioxide is released, causing the formulation to float in the stomach. Other approaches and materials that have been reported are a mixture of sodium alginate and sodium bicarbonate (Arrora S, *et al*, 2005),multiple unit floating pills that generate carbon dioxide when ingested, floating minicapsules with a core of sodium bicarbonate, lactose and polyvinylpyrrolidone coated with hydroxypropyl methylcellulose (HPMC), and floating systems based on ion exchange resin technology, etc.

a. Volatile liquid containing systems- These type of systems consist of two chambers separated by an impermeable, pressure-responsive, movable bladder. The first chamber contains the drug and the second chamber concotains the volatile liquid. The device inflates, and the drug is continuously released from the reservoir into the gastric fluid (Michaels, 1974).

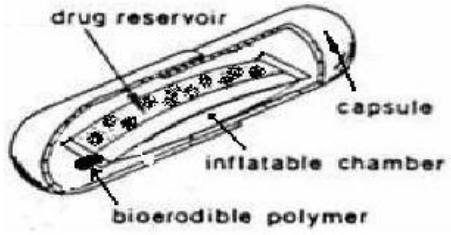


Fig. 5: Volatile liquid containing system

b.Gas – generating systems- These buoyant delivery systems utilize effervescent reaction between carbonate/bicarbonate salts and citric/tartaric acid to liberate CO2, which gets entrapped in the gellified hydrocolloid layer of the systems, thus decreasing its specific gravity and making it float over chyme(Ichikawa, etal., 1991)

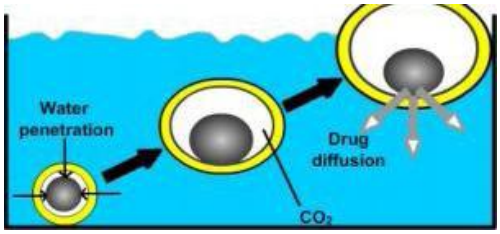


Fig.6: Principle mechanism of floating by CO_2 gas releasing method

2. BIO/MUCO–ADHESIVE SYSTEMS -

Bioadhesive drug delivery systems (BDDS) are used as a delivery device within the lumen to enhance drug absorption in a site-specific manner. This approach involves the use of bioadhesive polymers, which can adhere to the epithelial surface in the stomach (Dubernet C *et al*, 2004). Gastric mucoadhesion does not tend to be strong enough to impart to dosage forms the ability to resist the strong propulsion forces of the stomach wall. The continuous production of mucous by the gastric mucosa to replace the mucous that is lost through peristaltic contractions and the dilution of the stomach content also seem to limit the potential of mucoadhesion as a gastroretentive force. Some of the most promising excipients that have been used commonly in these systems include polycarbophil, carbopol, lectins, chitosan and gliadin, etc. (Moes AJ. Gast, *et al*, 1993).

Mechanism of bio/muco-adhesion- Binding of polymers to the mucin/epithelial surface can be devided into three categories:

a.Hydration – mediated adhesion- Certain hydrophilic polymers have the tendency to imbibe large amount of water and become sticky, thereby acquiring bioadhesive properties. The prolonged gastroretention of the bio/muco-adhesive delivery system is further controlled by the dissolution rate of the polymer.

b.Bonding –mediated adhesion- Adhesion of polymers to mucus/epithelial cell surface involves varying bonding mechanism. hysical or mechanical bonds can result from deposition and inclusion of the adhesive material in the crevices of the mucusa. Secondary chemical bonds, contributing to bioadhesive properties, consist of dispersive intractions (i.e. van der Walls intractions) and stronger specific intraction, which include hydrogen bonds. The hydrophilic functional groups responsible for forming hydrogen bonds are the hydroxyl (--OH) and the carboxylic groups (--COOH) (Chien,1992).

c.Receptor – mediated adhesion- Certain polymers have the ability to bind to specific receptor sites on the cell surface. The receptor mediated events serves as a potential approach in

bio/muco- adhesion, hence enhancing the gastric retention of dosage forms. Certain plant lectins, like tomato lectins, interact specifically with the sugar groups present in mucus or on the glycocalyx.(Sharma S et, al., 2006).

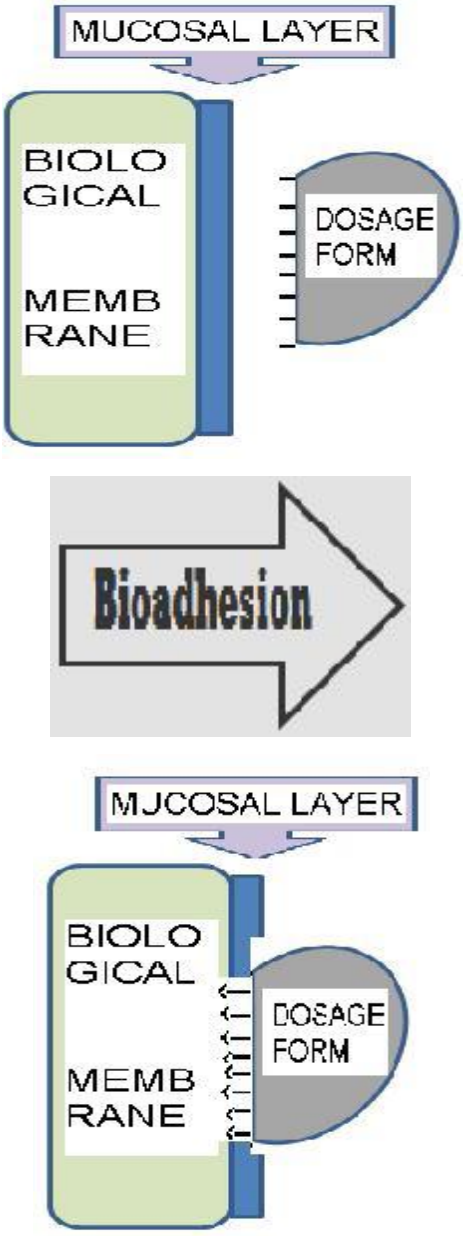


Fig. 7: Bio-adhesion system

3. SWELLING SYSTEMS - These are the dosage forms, which after swallowing, swell t an extent that prevents their exit from the pylorus. As a result, the dosage form is retained in the stomach for a long period of time. These systems may be named as "plug type systems", since they exibit the tendency to remain lodged at the pyloric sphincter. The formulation is designed for gastric retention and controlled delivery of the drug into the gastric cavity (Streubel A et. al., 2006). Such polymeric matrices remain in the gastric cavity for several hours even in the fed state. Sustained and controlled drug release may be achieved by selection of proper molecular weight polymer, and swelling of the polymer retards the drug release. On coming in contact with gastric fluid, the polymer imbibes water and swells. The extensive of these polymers is due to the presence of physical/chemical cross-links in the hydrophilic polymernetwork.(Gupta,etal.,2002).

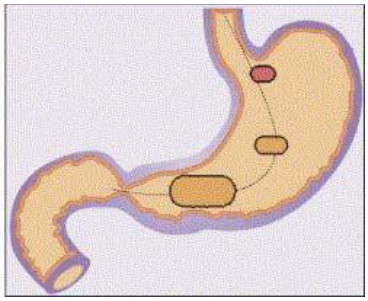


Fig. 8: Swellable tablet in stomach

4. HIGH DENSITY SYSTEMS-Sedimentation has been employed as a retention mechanism for pellets that are small enough to be retained in the rugae or folds of the stomach body near the pyloric region, which is the part of the organ with the lowest position in an upright posture. Dense pellets (approximately 3g/cm-3) trapped in rugae also tend to withstand the peristaltic movements of the stomach wall. With pellets, the GI transit time can be extended from an average of 5.8–25 hours, depending more on density than on the diameter of the pellets27. Commonly used excipients are barium sulphate, zinc oxide, titanium dioxide and iron powder, etc.These materials increase density by up to 1.5– 2.4g/cm-3.(Gehrke,1990).

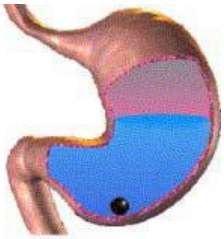


Fig. 9 : High density systems

5. **Magnetic Systems** - This approach to enhance the gastric retention time (GRT) is based on the simple principle that the dosage form contains a small internal magnet, and a magnet placed on the abdomen over the position of the stomach. Although magnetic system seems to work, the external magnet must be positioned with a degree of precision that might compromise patient compliance. (Whitehead, *et al*, 2000).

ADVANTAGES OF GASTRORETENTIVE DRUG DELIVERY SYSTEMS

Enhanced bioavailability the bioavailability of riboflavin CR-GRDF is significantly enhanced in comparison to the administration of non-GRDF CR polymeric formulations. There are several different processes, related to absorption and transit ofthe drug in the gastrointestinal tract, that act concomitantly to influence the magnitude of drug absorption (Klausner EA, *et al*, 2003).

Enhanced first-pass biotransformation In a similar fashion to the increased efficacy of active transporters exhibiting capacity limited activity, the pre-systemic metabolism of the tested compound may be considerably increased when the drug is presented to the metabolic enzymes (cytochrome P450, in particular CYP3A4) in a sustained manner, rather than by a bolus input. (Hoffman A, 1998).

Sustained drug delivery/reduced frequency of dosing For drugs with relatively short biological halflife, sustained and slow input from CR-GRDF may result in a flip-flop pharmacokinetics and enable reduced dosing frequency. This feature is associated with improved patient compliance, and thereby improves therapy.

Targeted therapy for local ailments in the upper GIT

The prolonged and sustained administration of the drug from GRDF to the stomach may be advantageous for local therapy in the stomach and small intestine. By this mode of administration ,therapeutic drug concentrations may be attained locally while systemic concentrations, following drug absorption and distribution, are minimal.

Reduced fluctuations of drug concentration

Continuous input of the drug following CRGRDF administration produces blood drug concentrations within a narrower range compared to the immediate release dosage forms. Thus, fluctuations in drug effects are minimized and concentration dependent adverse effects that are associated with peak concentrations can be prevented. This feature is of special importance for drugs with a narrow therapeutic index (*Hoffman A, 1999).*

Improved selectivity in receptor activation

Minimization of fluctuations in drug concentration also makes it possible to obtain certain selectivity in the elicited pharmacological effect of drugs that activate different types of receptors at different concentrations.

Reduced counter-activity of the body

In many cases, the pharmacological response which intervenes with the natural physiologic processes provokes a rebound activity of the body that minimizes drug activity. Slow input of the drug into the body was shown to minimize the counter activity leading to higher drug efficiency.

Extended time over critical (effective) concentration

For certain drugs that have non-concentration dependent pharmacodynamics, such as betalactam antibiotics, the clinical response is not associated with peak concentration, but rather with the duration of time over a critical therapeutic concentration. The sustained mode of administration enables extension of the time over a critical concentration and thus enhances the pharmacological effects and improves the clinical outcomes.

Minimized adverse activity at the colon

Retention of the drug in the GRDF at the stomach minimizes the amount of drug that reaches the colon. Thus, undesirable activities of the drug in colon may be prevented. This pharmacodynamic aspect provides the rationale for GRDF formulation for beta-lactam antibiotics that are absorbed only from the small intestine, and whose presence in the colon leads to the development of microorganism's resistance.

Site specific drug delivery

A floating dosage form is a feasible approach especially for drugs which have limited absorption sites in upper small intestine30. The controlled, slow delivery of drug to the stomach provides sufficient local therapeutic levels and limits the systemic exposure to the drug. This reduces side effects that are caused by the drug in the blood circulation. In addition, the prolonged gastric availability from a site directed delivery system may also reduce the dosing frequency.

Limitations-

GRDDS have potential in improving *BA* of drugs exhibiting 'absorption window'. However they have certain limitations. One of the major disadvantages of the floating system is the requirement of high levels of fluids in the stomach for the delivery system to float and work efficiently (Deshpande, *et al*, 1997).

1. Require a higher level of fluids in the stomach.
2. Not suitable for Drugs that...

a. Have solubility problems in gastric fluid.E.g. phenytoin

b. Cause G.I irritation. eg. NSAIDS.

c. Are unstable in acidic environment.

3. Drugs intended for selective release in the colon E.g. 5- amino salicylic acid and corticosteroids etc.
4. The floating systems in patients with achlorhydria can be questionable in case of swellable system.
5. Retention of high density systems in the antrum part under the migrating waves of the stomach is questionable.
6. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.
7. The mucus on the walls of the stomach is in a state of constant renewal, resulting in unpredictable adherence.

REVIEW OF LITERATURE

1. **Kumar *et al*** demonstrated works on the gastroretentive dosage forms for prolonging gastric residence time. In the study, the concepts of gastric emptying and absorption windows and current technological developments in gastroretentive drug delivery systems were discussed including their advantages and disadvantages alongwith various evaluation techniques and marketed products for gastroretentive drug delivery. According to the authors, the bioadhesive superporous hydrogel, floating and expanding systems showed the most promising potential for achieving the goal of gastroretention.

2. **El-Kamal *et al*** prepared and evaluated ketoprofen floating oral delivery system. They designed sustained release system for ketoprofen to increase its residence time in the stomach without contact with the mucosa which was achieved through the preparation of floating microparticles by the emulsion-solvent diffusion technique. They used four different ratios of Eudragit S100 with Eudragit RL to form the floating microparticles. It was found that release rates were generally low in 0.1 N HCl especially in presence of high content of Eudragit S100 while in phosphate buffer pH 6.8, high amounts of Eudragit S100 tended to give a higher release rate.

3. **Ali *et al*** formulated hydrodynamically-balanced system for metformin as a single unit-floating capsule.The formulation was optimized on the basis of in vitro buoyancy and in vitro release in simulated fed state gastric fluid. Effect of various release modifiers was studied to ensure the delivery of drug from the HBS capsules over a prolonged period. Capsules prepared with HPMC K4M and ethyl cellulose gave the best in vitro percentage release and were taken as the optimized formulation.

4. **Patel *et al*** developed and optimized a controlled- release multiunit floating system of ranitidine HCl sing compritol, gelucire 50/13 and geliucire 43/01 as lipid carriers. Ranitidine HCl lipid granules were prepared by the melt granulation technique and evaluated for in vitro floatinganddrugrelease. Ethylcellulose, methylcellulose and

hyroxypropyl methylcellulose were evaluated as release rate modifiers. They concluded that the hydrophobic lipid Gelucire 43/01 could be considered an effective carrier for design of a multiunit floating drug delivery system for highly water-soluble drugs such as ranitidine HCl.

5. **Sahoo *et al*** formulated floating microspheres of Ciprofloxacin HCl by cross-linking technique. A polymeric mixture of sodium alginate and hydroxy propyl methyl cellulose (HPMC) was used. Sodium bicarbonate was used as gas forming agent. The solution was dropped to 1% calcium chloride solution containing 10% acetic acid for carbon dioxide release and gel formation. The prepared floating microspheres were evaluated with respect to particle size distribution, floating behavior, drug content, entrapped morphology and in vitro release study. Effect of sodium bicarbonate on the above mentioned parameters were evaluated and it was found that sodium bicarbonate had a pronounced effect on various parameters.

6. **Choia *et al*** reported preparation of alginate beads for floating drug delivery system and studied the effects of CO2 gas forming agents. Floating beads were prepared from a sodium alginate solution containing CaCO3 or NaHCO3 as gas-forming agents. They studied the release characteristics of riboflavin as a model drug. Release rate of riboflavin increased proportionally with addition of NaHCO3. The results of these studies indicate that CaCO3 is superior to NaHCO3 as gas forming agent in alginate bead preparations.

7. **Sharma and Pawar et al** developed low-density multi particulate system for pulsatile release of meloxicam for which they combined the principles of floating and pulsatile drug delivery system. They prepared multi particulate floating pulsatile drug delivery system using porous calcium silicate and sodium alginate for time and site-specific drug release of Meloxicam.

8. **Jaimini *et al*** formulated and evaluated Famotidine floating tablets. They used Methocel K100 and Methocel K 15 M with effervescent mixture. It was observed that decrease in the citric acid level increased the floating lag time but tablets floated for longer duration.

A combination of sodium bicarbonate (130 mg) and citric acid (10mg) was found to achieve optimum in vitro buoyancy. They reported that tablets prepared with k 100 had longer floating time compared with formulations containing Methocel K15 M.

9. **Dave *et al*** reported a gastroretentive drug delivery system of ranitidine hydrochloride. Guar gum, xanthan gum, and hydroxy propyl methylcellulose were evaluated for gel forming properties. Sodium bicarbonate was incorporated as a gas-generating agent. They investigated the effect of citric acid and stearic acid on drug release profile and floating properties. They concluded that the proper balance between a release rate retardant and a release rate enhancer could produce a drug dissolution profile similar to a theoretical dissolution profile.

10. **Narendra *et al*** reported optimization of bilayer floating tablet containing metoprolol tartrate as a model drug for gastric retention. They employed a 23 factorial design in formulating the GFDDS with total polymer content-to-drug ratio (X1), polymer-to-polymer ratio (X2), and different viscosity grades of HPMC (X3) as independent variables. The results indicate that X1 andX2 significantly affected the floating time and release properties but the effect of different viscosity grades of HPMC (K4M and K10M) was non-significant.

11. **Sunil *et al*** prepared floating microspheres consisting of calcium silicate as porous carrier and Eudragit S as polymer by solvent evaporation method and evaluated their gastroretentive and controlled release properties. They studied the effect of various formulation and process variables on the particle morphology,micromeritic properties, in vitro percentage drug entrapment and in vitro drug release. Prolonged gastric residence time of over six hours was achieved in rabbits for calcium silicate based floating microspheres of orlistate. The enhanced elimination half-life observed after pharmacokinetic investigation is due to the floating nature of the designed formulations.

12. **Umamaheswari *et al*** prepared floating-bioadhesive microspheres containing acetohydroxamic acid for clearance of Helicobacter Pylori. They explored a synergism

between a floating and a bioadhesive system.Floating microspheres containing the antiurease drug acetohydroxamic acid were prepared by a novel quasi emulsion solvent diffusion method. The microballons were coated with 2% w/v solution of polycarbophil by the air suspension coating method. The results suggested that AHA-loaded floating microspheres were superior as potent urease inhibitor whereas urease plays an important role in the colonization of H. Pylori.

13. **Patel *et al*** developed ranitidine floating tablets; in which they optimized types of filler, different viscosity grades of HPMC and its concentration. Two fillers namely Avicel pH 102 and Tablettose 80 were used. Study revealed that type of filler had significant effect on release of drug from hydrophilic matrix tablets (f2 value 41.30) and floating properties. Three different viscosity grades of HPMC namely K100 LV, K4M and K15M were used. Viscosity had a major influence on drug release from hydrophilic matrices as well as on floating properties. The drug release from hydrophilic matrices occurred via diffusion mechanisms following square root of time profile. Hardness of tablets had greater influence on floating lag time which might be due to decreased porosity whereas the position of paddle and types of dissolution medium had no significant effect on drug release.

14. **Srivastava *et al*** prepared floating matrix tablets of atenolol to prolong gastric residence time and increase drug bioavailability. The tablets were prepared by direct compression technique, using polymers such as HPMC K15M, K4M, Guargum (GG), and sodium carboxy methylcellulose (SCMC), alone or in combination and other standard excipients. Tablets were evaluated for physical characteristics like hardness, swelling index, floating capacity, thickness and weight variation. The effect of effervescent on buoyancy and drug release pattern was also studied. In vitro release mechanism was evaluated by linear regression analysis. GG- and SCMC- based matrix tablets showed significantly greater swelling indices compared with other batches. The tablets exhibited controlled and prolonged drug release profiles while floating over the dissolution medium.

15. **Gohel *et al*** developed a more relevant in vitro dissolution method to evaluate a carbamazepine floating drug delivery systems. The glass beaker was modified by adding a side arm at the bottom of the beaker so that the beaker can hold 70 ml of 0.1 N HCl dissolution mediums and allow collection of samples. The tablet did not stick to the agitating device in the proposed dissolution method. The drug release followed zero order kinetics in the proposed method. The proposed test may show good in vitro in vivo correlation (IVIVC) since an attempt is made to mimic the in vivo conditions.

16. **Amin *et al*** developed a gastroretentive drug delivery system of ranitidine hydrochloride which was designed using guar gum, xanthan gum and HPMC. Sodium bicarbonate was incorporated as a gas-generating agent. The effect of citric acid and stearic acid on drug release profile and floating properties was investigated. The addition of stearic acid reduces the drug dissolution due to its hydrophobic nature. A 32 full factorial design was applied to systemically optimize the drug release profile and the results showed that a low amount of citric acid and a high amount of stearic acid favor sustained release of ranitidine HCl from a gastroretentive formulation.

17. **Streubel *et al*** prepared single-unit floating tablets based on polypropylene foam powder and matrix-forming polymer. Incorporation of highly porous foam powder in matrix tablets provided density much lower than the density of the release medium. A 17% w/w foam powder was achieved in vitro for at least 8 hours. It was concluded that varying the ratios of matrix-forming polymers and the foam powder could alter the drug release patterns effectively.

18. **Li *et al*** evaluated the contribution of formulation variables on the floating properties of a gastro floating drug delivery system using a continuous floating monitoring device and statistical experimental design. The formulation was conceived using 2x3 full factorial designs for calcium delivery. HPMC was used as a low- density polymer and citric acid was incorporated for gas generation. Analysis of variance (ANOVA) test on the results from these experimental designs demonstrated that the hydrophobic agent magnesium stearate could significantly improve the floating capacity of the delivery system. High-viscosity polymers had good effect on floating properties. The residual floating force

values of the different grades of HPMC were in the order K4 M~ E4 M~K100 LV> E5 LV but different polymers with same viscosity, i.e., HPMC K4M, HPMC E4M did not show any significant effect on floating property. Better floating was achieved at a higher HPMC/carbopol ratio and this result demonstrated that carbopol has a negative effect on the floating behavior.

19. **Sangekar *et al*** studied the effect of food and specific gravity on the gastric retention time of floating (spec. grav. 0.96) and non-floating (spec. grav. 1.59) tablet formulations was investigated using gamma scintigraphy in humans. The results obtained indicate that the presence of food in the stomach appears to significantly prolong gastric retention of both the floating and non- floating tablets while specific gravity does not seem to play an important role in the residency time of the tablets in the stomach.

20. **Xiaoqiang *et al*** developed hydrodynamically balanced sustained release tablets containing drug and hydrophilic hydrocolloids which on contact with gastric fluids at body temperature formed a soft gelatinous mass on the surface of the tablet and provided a water-impermeable colloid gel barrier on the surface of the tablets. The drug slowly released from the surface of the gelatinous mass that remained buoyant on gastric fluids.

21. **Rahman *et al*** developed a bilayer-floating tablet (BFT) for captopril using direct compression technology. HPMC, K-grade and effervescent mixture of citric acid and sodium bicarbonate formed the floating layer. The release layer contained captopril and various polymers such as HPMC-K15M, PVP-K30 and Carbopol 934p, alone or in combination with the drug. The floating behavior and in vitro dissolution studies were carried out in a USP 23 apparatus 2 in simulated gastric fluid (without enzyme, pH 1.2). Final formulation released approximately 95% drug in 24 h in vitro, while the floating lag time was 10 min and the tablet remained loatable throughout all studies. Final formulation followed the higuchi release model and showed no significant change in physical appearance, drug content, floatability or in vitro dissolution pattern after storage at 45 °C/75% RH for three months.

22. **Bomma *et al*** prepared floating matrix tablets of norfloxacin which were developed to prolong gastric residence time leading to an increase in drug bioavailability by using wet granulation technique using polymers such as HPMCK4M, HPMCK100M and Xanthan gum. The tablets exhibited controlled and prolonged drug release profile while floating over dissolution medium was confirmed as drug release mechanism from these tablets.

23. **Thakkar *et al*** formulated and evaluated the levofloxacin hemihydrate floating tablets that were prepared by direct compression method using gelucire 43/01 and HPMC polymers in different ratio. The in vitro release study revealed the fact that the release rate of drug was decreased by increasing the proportions of gelucire 43/01 by 5 to 40% matrix tablets containing 25% HPMCK4M and 15% gelucire 43/01.

24. **Rao *et al*** formulated and optimized the floating drug delivery system of cephalexin. Tablets were prepared by direct compression method incorporating HPMCK4M, xanthan gum, guar gum, sodium bicarbonate and tartaric acid as gas generating agent. The diffusion exponent of krosmeyer peppas for optimized formulation was found to be 0.635 which significantly indicated the mechanism of drug release.

25. **Rohilla Ankur *et al*** Gastroretentive drug delivery system has been a significant approach over the past few years that have been noted to prolong gastric residence time, thereby targeting site-specific drug release in the upper gastrointestinal (GI) tract for local or systemic effects. The present study has been investigated to compile the recent as well as past literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. Floating systems have been considered as one of the imperative categories of drug delivery systems with gastric retentive behavior. The review article explains the various floating drug delivery systems that are formulated in order to enhance the drug bioavailability. Moreover, various gastroretentive approaches designed and developed such as high density, floating, bioadhesive, super porous hydrogel and magnetic systems have been clearly discussed in the article.

26. **Sunil Kumar *et al*** The purpose of writing this review on gastroretentive drug delivery systems was to compile the recent literature with special focus on various gastroretentive approaches that have recently become leading methodologies in the field of site-specific orally administered controlled release drug delivery. In order to understand various physiological difficulties to achieve gastric retention, we have summarized important factors controlling gastric retention. Gastro retention would also facilitate local drug delivery to the stomach and proximal small intestine. Thus, gastroretention could help to provide greater availability of new products and consequently improved therapeutic activity and substantial benefits to patients. Controlled gastric retention of solid dosage form may be achieved by the mechanisms of floatation, mucoadhesion, sedimentation, expansion or by a modified shaped system.

27. **K.R. Vinod *et al*** Gastro retentive drug delivery systems were designed to prolong the gastric residence time in the stomach. The objective of the present study is to prepare the floating microspheres of Lansoprazole and sustain the drug release for longer time to overcome the short half life of the drug. Floating microspheres with four different variabilities in ratios of polymer and calcium carbonate were formulated by non-aqueous solvent evaporation method and in vitro evaluations were performed. Calcium carbonate acts as an effervescent agent as well as providing alkaline microenvironment for acid labile Lansoprazole. Drug: polymer 1:2 ratio gave the best result with 86.67% maximum release extended through a period of 11hrs. It was observed that as the polymer concentration along with calcium carbonate increases the buoyancy of microspheres also extended proportionally. SEM studies of microspheres showed good topology and the size was 355 μm. The cumulative % drug release in simulated gastric fluids after 10 hours was 71.3%- 86.67%. Model fitting analysis revealed the release pattern was following Korsmeyer-Peppas for all formulations by obtaining maximum r^2 value.

28. **A. M. Mahale *et al*** Sustained release micro particles are mainly oral dosage forms consisting of a multiplicity of small discrete units, the active substance is present as a number of small independent subunits with diameter of 0.05-2.00mm.These subunits like

pellets, microcapsules, microspheres are filled into a sachet and encapsulated or compressed into a tablet. There are many reasons for formulating a drug as a sustained release micro particles for example, to facilitate disintegration in the stomach, or to provide a convenient, fast disintegrating tablet that dissolves in water before swallowing which can aid compliance in older patients and children. Sustained release micro particles show better reproducible pharmacokinetic behavior than conventional (monolithic) formulations. The individual subunit particles pass rapidly through the GI tract. They provide many advantages over single unit systems because of their small size. Multiparticulates are less dependent on gastric empty ting, resulting in less inter and intra-subject variability in gastrointestinal transit time. They are also better distributed and less likely to cause local irritation. Recently much emphasis is being laid on the development of sustained release micro particles dosage forms in preference to single unit systems because of their potential benefits such as increased bioavailability, reduced risk of systemic toxicity, reduced risk of local irritation and predictable gastric emptying. Sustained release forms are designed for the normal population that is one the basis of average drug biological half lives. Consequently, Disease states that alter drug disposition, significant patient variation and so forth are not accommodated. Economical factors must be assessed since more costly process and equipment are involved in manufacturing.

29. **Mahesh Chavanpatil *et al*** Sustained release (SR)-gastroretentive dosage forms (GRDF) enable prolonged and continuous input of the drug to the upper parts of the gastrointestinal (GI) tract and improve the bioavailability of medications that are characterized by a narrow absorption window. A new strategy is proposed for the development of gastroretentive dosage forms for Ofloxacin preferably once daily. The design of the delivery system was based on the sustained release formulation, with floating and swelling features in order to prolong the gastric retention time of the drug delivery systems. Different polymers, such as psyllium husk, HPMC K100M, crospovidone and its combinations were tried in order to get the desired sustained release profile over a period of 24 h. Various formulations were evaluated for buoyancy lag time, duration of buoyancy, dimensional stability, drug content and in vitro drug release profile. It was found that dimensional stability of the formulation increases with the

increasing psyllium husk concentration. It was also found that in vitro drug release rate increased with increasing amount of crospovidone due to the increased water uptake, and hence increased driving force for drug release. The optimized formulation was subjected to stability studies at different temperature and humidity conditions as per ICH guidelines. In vivo studies were carried out for the optimized formulation in 24 healthy human volunteers and the pharmacokinetic parameters of developed formulations were compared with the marketed once daily (Zanocin) formulation. Based on the in vivo performance in a parallel study design in healthy subjects, the developed formulation shows promise to be bioequivalent to the marketed product (Zanocin). The percent relative bioavailability of developed formulation was found to be 97.55%.

30. **Veerareddy *et al*** The aim of the present investigation was to develop and evaluate gastroretentive drug delivery tablets (GRDDTs) of Ofloxacin using different polymers such as HPMC K4M, HPMC K15M, Polyethylene oxide WSR 303, Carbopol 971P, Xanthan Gum in different ratios for local action in gastric region to eradicate *Helicobacter pylori* infection. The GRDDTs were prepared by wet granulation method and evaluated for physical characteristics such as hardness, thickness, friability, drug content and floating properties. The optimized formula F4 showed better sustained drug release and which also had good floating properties and fitted best to be Korsmeyer-Peppas model with R2 value of 0.9848. As the n value for the Korsmeyer- Peppas model was found be less than 0.45 it follows Fickian diffusion mechanism. FT-IR result showed that there is no drug excipient interaction. *In vivo* radiographic studies were conducted with BaSO4 loaded tablets to examine the increased gastric residence time of the prepared tablets. The study revealed that the tablet remained in the stomach for 300±10min which indicates the increase in the gastric residence time for the effective localized action of the Ofloxacin in the treatment of *Helicobacter pylori* caused peptic ulcer.
31. **D. Saravanan *et al*** The present study outlines a systematic approach for designing and development of Ofloxacin floating tablets to enhance the bioavailability and therapeutic efficacy of the drug. Floating tablets of Ofloxacin have shown controlled release thereby proper duration of action at a particular site and are designed to prolong the gastric residence time after oral administration. Different formulations were formulated by wet

granulation technique using HPMC K4M, HPMC K15M and HPMC K100M (floating agent) as polymers along with sodium bicarbonate as gas generating agent. The formulations were evaluated for their physicochemical properties, buoyancy lag time, total floating time, swelling index and *invitro* drug release. It was found that the hardness of the tablets affects the Buoyancy characteristic of the dosage form. All six formulations possessed good floating properties with total floating time between 8 – 12 hrs. The *invitro* cumulative % drug release of the formulations F1A, F1B, F2A, F2B, F3A and F3B were 102.85%, 101.32%, 100.2%, 99.98%, 99.28% and 97.25%.

32. **Golam Kibria *et al*** Extended release formulation of alfuzosin, an α-antagonist used for prostatic hypertrophy, is available in market. It is convenient for older patients to take only one tablet a day. Marketed alfuzosin formulation is three layered geomatrix tablet that requires special facilities, high cost, more time and complex operation than normal direct compression formulation. Therefore, a less complicated formulation is desired which can be prepared by conventional tools. The aim of the study was the development and *in vitro* evaluation of a controlled release dosage form of a freely soluble weakly basic drug (alfuzosin hydrochloride). Binary mixer of one hydrophilic polymer (hydroxypropyl methylcellulose) and one hydrophobic polymer (ethyl cellulose) was used in tablets prepared by direct compression, 32 factorial design was chosen and the amount of two polymers were taken as independent variables. The percent drug released at 1, 6, 12, and 20 h were selected as response. The main effect and interaction terms were quantitatively evaluated using mathematical model. Dissolution data were fitted to zero order, first order, and Higuchi's release kinetics to evaluate kinetic data. According to Korsmeyer's equation drug release followed both diffusion and erosion mechanism in all cases. Drug release was different from three fillers (microcrystalline cellulose, lactose and dibasic calcium phosphate).

33. **Sandeep Gummudavelly *et al*** floating matrix tablets of Alfuzosin hydrochloride were developed to prolong gastric residence time. Alfuzosin hydrochloride was chosen as a model drug because it is poorly absorbed from the lower gastrointestinal tract. The tablets were prepared by direct compression and melt granulation technique, using polymers such as hydroxy propyl methyl cellulose K15M, sodium carboxy methyl cellulose,

compritol 888 ATO and either alone or in combination, and other standard excipients. Tablets were evaluated for physical characteristics hardness, % friability, floating capacity, weight variation, content uniformity, in-vitro release characteristics for 12 hours and in-vivo gastic retention time. In-vitro release mechanism was evaluated by linear regression analysis. The calculated regression coefficients value of higuchi and koresemayer (0.998, n value 0.520) for optimized formulation F2 and the drug release mechanism was found to be non-ficikian diffusion. No drug-polymer interaction was observed by Fourier Transform Infrared Spectra Analysis. In-vivo studies showed that the tablets retained in stomach for 6hours. It was concluded that, HPMC K15M alone retarded the drug release for highly water soluble drug (Alfuzosin hydrochloride) for a period of 12 hours.

34. **Sreenivasa Reddy *et al*** alfuzosin Hydrochloride extended release tablets ere prepared by wet granulation method by using natural and synthetic polymers Guar gum, Eudragit RLPO and Hypromellose (Methocel K100M). The present study was to develop stable and robust formulation of Alfuzosin Hydrochloride ER tablets 10mg. The formulation containing binary mixer of Hypromellose at 31.0 % and Guar gum at 11.0 % were evaluated for various physicochemical parameters by official procedures showed consistent results. The in-vitro release study of tablets was carried out in 0.01N HCL for 20 hours. A time (hr.) interval 1, 2, 6, 12, and 20 has showed the best formulation releases when compared with the reference product. Both the diffusion and erosion mechanisms were responsible for drug release as shown by the power law. Dissolution data were fitted to zero order, first order, Higuchi's, Peppas & Korsmeyer,Hixson Crowell, Weibull and Baker Lonsdale release kinetics to evaluate kinetic data. The main effect and interaction terms were quantitatively evaluated using mathematical model. Hence the gradual release of Alfuzosin Hydrochloride over a prolonged time period of 20 hr. which indicates the usefulness of the formulation for once daily dosage form. Optimized formulation was found stable during accelerated stability study for 3 months at 40°C± 2°&75%±5 % RH.
35. **Prashant Khemariya *et al*** the objective of this research work was to formulate and evaluate the floating drug delivery system containing *Ofloxacin* as a model drug and to optimize the drug release profile. Ofloxacin is a slightly water-soluble drug and having

absorption only in upper part of GI tract (up to jejunum). Ofloxacin tablets were prepared by dry granulation technique which containing HPMC K100M, xanthan gum, carbopol 934P, PVP K30, MCC, lactose, aerosil, and gas generating agent such as sodium bicarbonate were taken as independent variables. The compressed matrix tablets were evaluated for various parameters like hardness, friability, weight variation, uniformity of drug. Result shows the drug content was uniform in all the formulations of the prepared tablets. *In vitro* drug release pattern was evaluated by using USP-I (Basket) apparatus containing 0.1 N HCl and Simulated gastric fluid. The optimized formulation containing Ofloxacin-800 mg, HPMC K-15- M-5 mg, xanthan gum-12.5 to 24 mg, aerosol-1 mg, Mg Stearate- 9+4 mg and sodium bicarbonate- 80 mg has displayed almost zero order release kinetics with a floating lag time of between 10 sec. to 56 sec. The effect of formulation variables namely, different excipients, different polymers, and concentration of polymer were studied.

AIM AND OBJECTIVE

The alfuzosin of the present investigation is designed to retain in the stomach and deliver the drug alfuzosin for longer periods of time. The developed floating provides increased absorption of the alfuzosin at a rate such that effective plasma levels can be achieved and maintained for a prolonged duration.

The tablets were found to be floating immediately upon contact with the release medium showing no lag times in floating behavior because of the low density material. Extended floating times are achieved due to the air entrapped within the drug particles. This system provides more reliable retention for prolonged period of time compared to the other gastric retention systems.

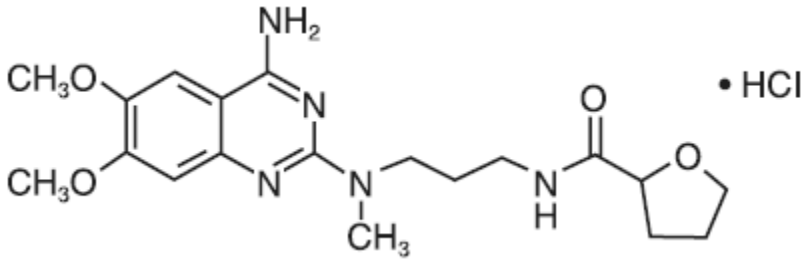
Floating of alfuzosin was formulated with HPMC to retain the tablet dosage form in the stomach and to release the drug in a controlled manner for increasing the oral bioavailability of the alfuzosin. In the present work direct compression method were used to prepare floating matrix tablets of alfuzosin.

PLAN OF WORK

- Literature Survey.
- Preformulation Studies
  1) Bulk density
  2) True density
  3) Carrs's index
  4) Hausners ratio
  5) Angle of repose
  6) Hardness
  7) Friability
  8) Thickness
  9) Log Float time
  10) Bouncy time
  11) Content uniformity
- Selection of Excipients.
  1) Hydroxy Propyl methylcellulose
  2) Carbopol940p
- Compatibility tests.
  1) FT IR
- Prototype Formulation (Lab Scale Development).
- Preparation of granules by direct compression method.
- The best formulation was selected based on available Preformulation formulation. Studies.
- To carry out the *Invitro* release studies for a period of 12hours.
- Stability studies were carried out as per the ICH guidelines for a period of 90days.

DRUG PROFILE

❖ **Alfuzosin**



Introduction:

1. Drug Name: Alfuzosin

2. Mechanism of Action: Alfuzosin is a non-subtype specific alpha(1)-adrenergic blocking agent that exhibits selectivity for alpha(1)-adrenergic receptors in the lower urinary tract. Inhibition of these adrenoreceptors leads to the relaxation of smooth muscle in the bladder neck and prostate, resulting in the improvement in urine flow and a reduction in symptoms in benign prostate hyperplasia. Alfuzosin also inhibits the vasoconstrictor effect of circulating and locally released catecholamines (epinephrine and norepinephrine), resulting in peripheral vasodilation

3. Dosage: 10mg ER tablets.

4. Uses:

Benign Prostatic Hyperplasia (BPH)

Reduction of urinary obstruction and relief of associated manifestations (e.g., hesitancy, interrupted or weak stream, sensation of incomplete bladder emptying or straining, urgency, nocturia) in patients with symptomatic BPH.

Although drug therapy usually is not as effective as surgical therapy, it may provide adequate symptomatic relief with fewer and less serious adverse effects compared with surgery.

May consider combined therapy with a α_1-adrenergic blocker and 5α-reductase inhibitor for men with bothersome moderate to severe BPH and demonstrable prostatic enlargement. Has been more effective than therapy with either drug alone in preventing long-term BPH symptom progression. Men at risk for BPH progression are most likely to benefit from combination therapy.

Physicochemical Properties:

1. Description: Alfuzosin (INN, provided as the hydrochloride salt) is an alpha-adrenergic blocker used to treat benign prostatic hyperplasia (BPH). It works by relaxing the muscles in the prostate and bladder neck, making it easier to urinate.
2. IUPAC Name: N-{3-[(4-amino-6,7-dimethoxyquinazolin-2-l)(methyl)amino]propyl}oxolane-2-carboxamide
3. Molecular Formula: $C_{19}H_{27}N_5O_4$4. Molecular Weight: Average: 389.4488
4. Monoisotopic: 389.206304377
5. Solubility: solubility: H2O: soluble0.3 mg/mL DMSO: soluble18 mg/mL Ethanol: soluble3.4 mg/mL.
6. Physical Form: White powder.
7. Melting point: 225^{o}C
8. Stability: 40 days
9. Categories: Antihypertensive Agents Adrenergic alpha-Antagonists

Pharmacokinetic Properties:

1. Half life ($t_{1/2}$): 10 hours (biological).
2. Shelf-Life: 36 months.
3. Bioavailability: 50
4. P^{H}: 2.2-2.
5. P^{Ka} : 0
6. Protein Binding: 82-90%

7. Route of Metabolism: Hepatic. Alfuzosin undergoes extensive metabolism by the liver, with only 11% of the administered dose excreted unchanged in the urine. Alfuzosin is metabolized by three metabolic pathways: oxidation, O-demethylations, and N-dealkylation. The metabolites are not pharmacologically active. CYP3A4 is the principal hepatic enzyme isoform involved in its metabolism.
8. *Route of Elimination:* Following oral administration of 14C-labeled alfuzosin solution, the recovery of radioactivity after 7 days (expressed as a percentage of the administered dose) was 69% in feces and 24% in urine.
9. *Volume of distribution:* 3.2 L/kg [healthy male middle-aged volunteers]

Food Interactions

Take after a meal (always the same meal), product bioavailability is reduced when taken on an empty stomach.

DRUG INTERACTIONS

Conivaptan CYP3A4 Inhibitors (Strong) may increase the serum concentration of Alfuzosin. Concomitant use of alfuzosin with a strong CYP3A4 inhibitor is a listed contraindication according to alfuzosin prescribing information.

Itraconazole the antifungal increases the effect of alfuzosin

Ketoconazole the antifungal increases the effect of alfuzosin

Ritonavir increases the effect/toxicity of alfuzosin

Tadalafil may enhance the hypotensive effect of Alfusozin. Monitor for hypotension during concomitant therapy.

Tamsulosin Concomitant use of alpha1-adrenergic antagonists, Tamsulosin and Alfuzosin, may result in additive antihypertensive effects. Combination therapy is not recommended. Telithromycin Telithromycin may reduce clearance of Alfuzosin. Consider alternate therapy. Terazosin Additive antihypertensive effects may occur. Increase risk of orthostatic hypotension and syncope. Concomitant therapy should be avoided.

Vardenafil Additive hypotensive effects of the PDE5 inhibitor, Vardenafil, and alpha1-blocker, Alfuzosin, may occur. Monitor for hypotension during concomitant therapy.

Voriconazole a strong CYP3A4 inhibitor, may increase the serum concentration of alfuzosin by decreasing its metabolism. Use of alfuzosin with strong CYP3A4 inhibitors is contraindicated by the manufacturer.

POLYMER PROFILE

Hypromellose

1. Nonproprietary Names

BP: Hypromellose

JP: Hypromellose

PhEur: Hypromellose

USP: Hypromellose

2. Synonyms

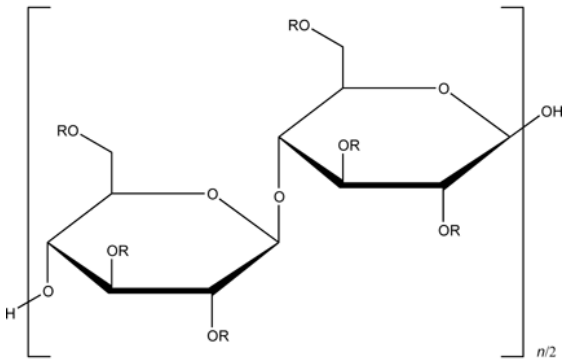
Benecel MHPC; E464; hydroxypropyl methylcellulose; HPMC; hypromellosum; Methocel; methylcellulose propylene glycol ether; methyl hydroxypropylcellulose; Metolose; MHPC; Pharmacoat; Tylopur; Tylose MO.

3. Chemical Name and CAS Registry Number :Cellulose hydroxypropyl methyl ether [9004-65-3]

4. Empirical Formula and Molecular Weight

The PhEur 6.3 describes hypromellose as a partlyO-methylated and O-(2-hydroxypropylated) cellulose. It is available in several grades that vary in viscosity and extent of substitution. Grades may be distinguished by appending a number indicative of the apparent viscosity, in mPa s, of a 2% w/w aqueous solution at 208C. Hypromellose defined in the USP 32 specifies the substitution type by appending a four-digit number to the nonproprietary name: e.g. hypromellose 1828. The first two digits refer to the approximate percentage content of the methoxy group (OCH3). The second two digits refer to the approximate percentage content of the hydroxypropoxy group (OCH2CH(OH)CH3), calculated on a dried basis. It contains methoxy and hydroxypropoxy groups conforming to the limits for the various types of hypromellose;Molecular weight is approximately 10 000–1 500 000.

5. Structural Formula



Where R is H, CH3, or CH3CH(OH)CH2

6. Functional Category

Bioadhesive material; coating agent; controlled-release agent;dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; release-modifying agent; solubilizing agent; stabilizing agent; suspending agent; sustained-release agent; tablet binder; thickening
agent; viscosity-increasing agent.

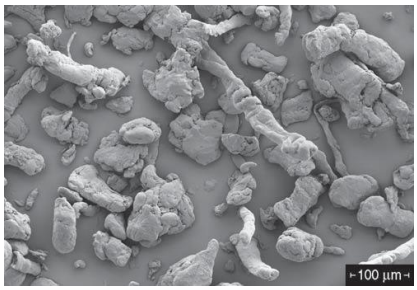
7 Applications in Pharmaceutical Formulation or Technology

Hypromellose is widely used in oral, ophthalmic, nasal, and topical pharmaceutical formulations.In oral products, hypromellose is primarily used as a tablet binder,(1) in film-coating,(2–7) and as a matrix for use in extendedrelease tablet formulations.(8–12) Concentrations between 2% and 5% w/w may be used as a binder in either wet- or dry-granulation processes. High-viscosity grades may be used to retard the release of drugs from a matrix at levels of 10–80% w/w in tablets and capsules. Hypromellose is also used in liquid oral dosage forms as a suspending and/or thickening agent at concentrations ranging from 0.25–5.0%.Depending upon the viscosity grade, concentrations of 2–20% w/w are used for film-forming solutions to film-coat tablets.Lowerviscosity grades are used in aqueous film-coating

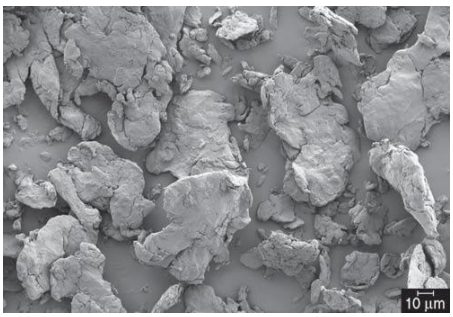
solutions, while Hypromellose higher-viscosity grades are used with organic solvents. Examples of film-coating materials that are commercially available include AnyCoat C, Spectracel, Pharmacoat, and the Methocel E Premium LV series.Hypromellose is also used as a suspending and thickening agent in topical formulations. Compared with methylcellulose, hypromellose produces aqueous solutions of greater clarity, with fewer undissolved fibers present, and is therefore preferred in formulations for ophthalmic use. Hypromellose at concentrations between 0.45–1.0% w/w may be added as a thickening agent to vehicles for eye drops and artificial tear solutions. It is also used commercially in liquid nasal formulations at a concentration of 0.1%. Hypromellose is used as an emulsifier, suspending agent, and stabilizing agent in topical gels and ointments. As a protective colloid, it can prevent droplets and particles from coalescing or agglomerating, thus inhibiting the formation of sediments. In addition, hypromellose is used in the manufacture of capsules, as an adhesive in plastic bandages, and as a wetting agent for hard contact lenses. It is also widely used in cosmetics and food products.

Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

SEM 1: Excipient: Methocel E5; manufacturer: Dow Wolff Cellulosics; magnification: 200_; voltage: 3 kV.



SEM 2: Excipient: Methocel K4M; manufacturer: Dow Wolff Cellulosics; magnification: 500_; voltage: 3 kV.



9. Typical Properties

Acidity/alkalinity pH = 5.0–8.0 for a 2% w/w aqueous solution.

Ash-41.5%

Autoignition temperature- 360^{o}C

Density (bulk)-0.341 g/cm3

Density (tapped)- 0.557 g/cm3

Density (true)-1.326 g/cm3

Melting point Browns at 190–2008C; chars at 225–2308C. Glass

Transition Temperature is 170–1808C.

Moisture content Hypromellose absorbs moisture from the atmosphere; the amount of water absorbed depends upon the initial

moisture content and the temperature and relative humidity of the surrounding air.

Solubility Soluble in cold water, forming a viscous colloidal solution; practically insoluble in hot water, chloroform, ethanol

(95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Certain grades of hypromellose are soluble in aqueous acetone solutions, mixtures of dichloromethane and propan-2-ol, and other organic solvents. Some grades are swellable in ethanol.

Specific gravity 1.26

Viscosity (dynamic)

A wide range of viscosity types are commercially available. Aqueous solutions are most commonly prepared, although hypromellose may also be dissolved in aqueous alcohols such as ethanol and propan-2-ol provided the alcohol content is less than 50% w/w. Dichloromethane and ethanol mixtures may also be used to prepare viscous hypromellose solutions.

Solutions prepared using organic solvents tend to be more viscous; increasing concentration also produces more viscous solutions

10 Stability and Storage Conditions

Hypromellose powder is a stable material, although it is hygroscopic after drying. Solutions are stable at pH 3–11. Hypromellose undergoes a reversible sol–gel transformation upon heating and cooling, respectively. The gelation temperature is 50–908C, depending upon the grade and concentration of material. For temperatures below the gelation temperature, viscosity of the solution decreases as temperature is increased. Beyond the gelation temperature, viscosity increases as temperature is increased.

Aqueous solutions are comparatively enzyme-resistant, providing good viscosity stability during long-term storage.(15) However, aqueous solutions are liable to microbial spoilage and should be preserved with an antimicrobial preservative: when hypromellose is used as a viscosity-increasing agent in ophthalmic solutions, benzalkonium chloride is commonly used as the preservative. Aqueous solutions may also be sterilized by autoclaving; the coagulated polymer must be redispersed on cooling by shaking. Hypromellose powder should be stored in a well-closed container, in a cool, dry place.

11 Incompatibilities

Hypromellose is incompatible with some oxidizing agents. Since it is nonionic, hypromellose will not complex with metallic salts or ionic organics to form insoluble precipitates.

12 Method of Manufacture

A purified form of cellulose, obtained from cotton linters or wood pulp, is reacted with sodium hydroxide solution to produce a swollen alkali cellulose that is chemically more reactive than untreated cellulose. The alkali cellulose is then treated with chloromethane and propylene oxide to produce methyl hydroxypropyl ethers of cellulose. The fibrous reaction product is then purified and ground to a fine, uniform powder or granules. Hypromellose can then be exposed to anhydrous hydrogen chloride to induce depolymerization, thus producing low viscosity grades.

13 Safety

Hypromellose is widely used as an excipient in oral, opthalmic, nasal, and topical pharmaceutical formulations. It is also used extensively in cosmetics and food products.

Hypromellose is generally regarded as a nontoxic and nonirritating material, although excessive oral consumption may have a laxative effect.The WHO has not specified an acceptable daily intake for hypromellose since the levels consumed were not considered to represent a hazard to health. In fact, high dosages of hypromellose are being investigated for treating various metabolic syndromes.

14 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Hypromellose dust may be irritating to the eyes, so eye protection is recommended. Excessive dust generation should be avoided to minimize the risks of explosion. Hypromellose is combustible.

Nominal viscosity (mPa s)
Methocel K3 Premium LV
Methocel K100 Premium LVEP
Methocel K4M Premium
Methocel K15M Premium
Methocel K100M Premium
Methocel E3 Premium LV
Methocel E5 Premium LV
Methocel E6 Premium LV
Methocel E15 Premium LV
Methocel E50 Premium LV
Methocel E4M Premium
Methocel E10M Premium CR
Methocel F50 Premium
Methocel F4M Premium
Metolose 60SH 2910 50, 4000, 10 000
Metolose 65SH 2906 50, 400, 1500, 4000
Metolose 90SH 2208 100, 400, 4000, 15 000

17 Related Substances

Ethylcellulose; hydroxyethyl cellulose; hydroxyethylmethyl cellulose; hydroxypropyl cellulose; hypromellose acetate succinate; hypromellose phthalate; methylcellulose.

CARBOMER

1 Nonproprietary Names

BP: Carbomers

PhEur: Carbomers

USP-NF: Carbomer

2 Synonyms

Acrypol; Acritamer; acrylic acid polymer; carbomera; Carbopol; carboxy polymethylene; polyacrylic acid; carboxyvinyl polymer; Pemulen; Tego Carbomer.

3 Chemical Name and CAS Registry Number

Carbomer [9003-01-4]

Note that alternative CAS registry numbers have been used for carbomer 934 ([9007-16-3]), 940 ([9007-17-4]) and 941 ([9062-04-08]). The CAS registry number [9007-20-9] has also been used for carbomer.

4 Empirical Formula and Molecular Weight

Carbomers are synthetic high-molecular-weight polymers of acrylic acid that are crosslinked with either allyl sucrose or allyl ethers of pentaerythritol. They contain between 52% and 68% of carboxylic acid (COOH) groups calculated on the dry basis. The BP 2009 and PhEur 6.4 have a single monograph describing carbomer; the USP32–NF27 contains several monographs escribing individual carbomer grades that vary in aqueous viscosity, polymer type, and polymerization solvent. The molecular weight of carbomer is theoretically estimated at 7 _ 105 to 4 _ 109. In an effort to measure the molecular weight between crosslinks, MC, researchers have extended the network theory of elasticity to swollen gels and have utilized the inverse relationship between the elastic modulus and MC.(1–3) Estimated MC values of 237 600 g/mol for Carbopol 941 and of 104 400 g/mol for Carbopol 940 have been reported. In general,

carbomer polymers with lower viscosity and lower rigidity will have higher MC values. Conversely, higher-viscosity, more rigid carbomer polymers will have lower MC values.

5 Structural Formula

Carbomer polymers are formed from repeating units of acrylic acid. The monomer unit is shown above. The polymer chains are

crosslinked with allyl sucrose or allyl pentaerythritol.

6 Functional Category

Bioadhesive material; controlled-release agent; emulsifying agent;emulsion stabilizer; rheology modifier; stabilizing agent; suspending agent; tablet binder.

7 Applications in Pharmaceutical Formulation or Technology

Carbomers are used in liquid or semisolid pharmaceutical formulations as rheology modifiers. Formulations include creams, gels, lotions and ointments for use in ophthalmic, rectal,topical and vaginal preparations. Carbomer grades with residual benzene content greater than 2 ppm do not meet the specifications of the PhEur 6.4 monograph. However, carbomer having low residuals of other solvents than the ICH-defined 'Class I OVI solvents' may be used in Europe. Carbomer having low residuals of ethyl acetate, such as Carbopol 971P NF or Carbopol 974P NF, may be used in oral preparations, in suspensions, capsules or tablets.(23–35) In tablet formulations, carbomers are used as controlled release agents and/or as binders. In contrast to linear polymers, higher viscosity does not result in slower drug release with carbomers. Lightly crosslinked carbomers (lower viscosity) are generally more efficient in controlling drug release than highly crosslinked carbomers (higher viscosity). In wet granulation processes, water, solvents or their mixtures can be used as the granulating fluid. The tackiness of the wet mass may be reduced by including talc in the formulation or by adding certain cationic species to the granulating fluid. However, the presence of cationic salts may accelerate drug release rates and reduce bioadhesive properties. Carbomer polymers have also been investigated in the preparation of sustained-release matrix beads, as enzyme inhibitors of intestinal proteases in peptide-containing dosage forms, as a bioadhesive for a cervical patch and for intranasally administered microspheres, in magnetic granules for site-specific drug delivery to the esophagus, and in oral mucoadhesive controlled drug delivery systems. Carbomers copolymers are also employed as emulsifying agents in the preparation of oil-in-water emulsions for external administration.

Carbomer 951 has been investigated as a viscosity-increasing aid in the preparation of multiple emulsion microspheres. Carbomers are also used in cosmetics. Therapeutically, carbomer formulations have proved efficacious in improving symptoms of moderate-to-severe dry eye syndrome.

Table I: Uses of carbomers.

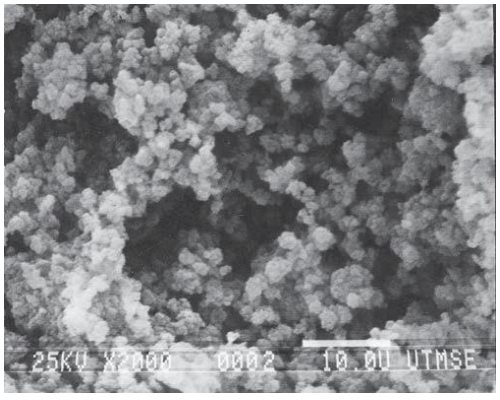
Use	Concentration (%)
Emulsifying agent	0.1–0.5
Gelling agent	0.5–2.0
Suspending agent	0.5–1.0
Tablet binder	0.75–3.0
Controlled-release agent	5.0–30.0

8 Description

Carbomers are white-colored, 'fluffy', acidic, hygroscopic powders with a characteristic slight odor. A granular carbomer is also
available (Carbopol 71G).

SEM 1: Excipient: Carbopol 971P; manufacturer: Lubrizol Advanced

Materials, Inc.; magnification: 2000_; voltage: 25 kV



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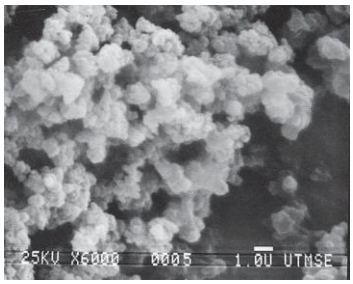
SEM 2: Excipient: Carbopol 971P; manufacturer: Lubrizol Advanced Materials, Inc.; magnification: 6000_; voltage: 25 kV.



*Aqueous viscosity (*mPa s) 300–115 000

Carbomer 934 (0.5% w/v) — 30 500–39 400

Carbomer 934P (0.5% w/v) — 29 400–39 400

Carbomer 940 (0.5% w/v) — 40 000–60 000

Carbomer 941 (0.5% w/v) — 4 000–11 000

Carbomer 1342 (1.0% w/v) — 9 500–26 500

Carbomer copolymer (1% w/v)

Type A — 4 500–13 500

Type B — 10 000–29 000

Type C — 25 000–45 000

Carbomer homopolymer (0.5% w/v)

Type A — 4 000–11 000

Type B — 25 000–45 000

Type C — 40 000–60 000

Carbomer interpolymer

Type A (0.5% w/v) — 45 000–65 000

Type B (1% w/v) — 47 000–77 000

Type C (0.5% w/v) — 8 500–16 500

Loss on drying 43.0% 42.0%

Sulfated ash 44.0% —

Residue on ignition — 44.0%(a)

Heavy metals 420 ppm 40.002%

Benzene 42 ppm þ

Carbomer 934 — 40.5%

Carbomer 934P — 40.01%

Carbomer 940 — 40.5%

Carbomer 941 — 40.5%

Carbomer 1342 — 40.2%

Carbomer copolymer — 40.0002%

Carbomer homopolymer — 40.0002%

Carbomer interpolymer — 40.0002%

Free acrylic acid 40.25% 40.25%(b)

Ethylacetate — þ

Carbomer copolymer — 40.5%

Carbomer homopolymer — 40.5%

Carbomer interpolymer — 40.35%

Cyclohexane — þ

Carbomer copolymer — 40.3%

Carbomer homopolymer — 40.3%

Carbomer interpolymer — 40.15%

9 Typical Properties

Acidity/alkalinity

pH = 2.5–4.0 for a 0.2% w/v aqueous dispersion; pH = 2.5–3.0 for Acrypol 1% w/v aqueous dispersion.

Density (bulk) 0.2 g/cm3 (powder); 0.4 g/cm3 (granular).

Density (tapped) 0.3 g/cm3 (powder); 0.4 g/cm3 (granular).

Dissociation constant pKa = 6.0_0.5

Glass transition temperature 100–1058C

Melting point Decomposition occurs within 30 minutes at 2608C.

Moisture content Typical water content is up to 2% w/w. However, carbomers are hygroscopic and a typical equilibrium

moisture content at 258C and 50% relative humidity is 8–10% w/w. The moisture content of a carbomer does not affect its

thickening efficiency, but an increase in the moisture content makes the carbomer more difficult to handle because it is less readily dispersed.

10 Stability and Storage Conditions

Carbomers are stable, hygroscopic materials that may be heated at temperatures below 1048C for up to 2 hours without affecting their thickening efficiency. However, exposure to excessive temperatures can result in discoloration and reduced stability. Complete decomposition occurs with heating for 30 minutes at 2608C. Dry powder forms of carbomer do not support the growth of molds and fungi. In contrast, microorganisms grow well in unpreserved aqueous dispersions, and therefore an antimicrobial preservative such as 0.1% w/v chlorocresol, 0.18% w/v methylparaben–0.02% w/v propylparaben, or 0.1% w/v thimerosal should be added. The addition of certain antimicrobials, such as benzalkonium chloride or sodium benzoate, in high concentrations (0.1% w/v) can cause cloudiness and a reduction in viscosity of carbomer dispersions. Aqueous gels may be sterilized by autoclaving(7) with minimal changes in viscosity or pH, provided care is taken to exclude oxygen from the system, or by gamma irradiation, although this technique may increase the viscosity of the formulation.(54,55) At room temperature, carbomer dispersions maintain their viscosity during storage for prolonged periods. Similarly, dispersion viscosity is maintained, or only slightly reduced, at elevated storage temperatures if an antioxidant is included in the formulation or if the dispersion is stored protected from light. Exposure to light causes oxidation that is reflected in a decrease in dispersion viscosity. Stability to light may be improved by the addition of 0.05–0.1% w/v of a water-soluble UV absorber such as benzophenone-2 or benzophenone-4 in combination with 0.05–0.1% w/v edetic acid. Carbomer powder should be stored in an airtight, corrosionresistant container and protected from moisture. The use of glass, plastic, or resin-lined containers is recommended for the storage of formulations containing carbomer.

11 Incompatibilities

Carbomers are discolored by resorcinol and are incompatible with phenol, cationic polymers, strong acids, and high levels of electrolytes. Certain antimicrobial adjuvants should also be avoided or used at low levels, see Section 11. Trace levels of iron and other transition metals can catalytically degrade carbomer dispersions. Certain amino-functional actives form complexes with carbomer; often this can be prevented by adjusting the pH of the dispersion

and/or the solubility parameter by using appropriate alcohols and polyols. Carbomers also form pH-dependent complexes with certain polymeric excipients. Adjustment of pH and/or solubility parameter can also work in this situation.

12 Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Excessive dust generation should be minimized to avoid the risk of explosion (lowest explosive concentration is 130 g/m3). Carbomer dust is irritating to the eyes, mucous membranes, and respiratory tract. In the event of eye contact with carbomer dust, saline should be used for irrigation purposes. Gloves, eye protection, and a dust respirator are recommended during handling. A solution of electrolytes (sodium chloride) is recommended for cleaning equipment after processing carbomers.

13 Related Substances

Polycarbophil.

CARBOXYMETHYLCELLULOSE SODIUM

1 Nonproprietary Names

BP: Carmellose Sodium

JP: Carmellose Sodium

PhEur: Carmellose Sodium

USP: Carboxymethylcellulose Sodium

2 Synonyms

Akucell; Aqualon CMC; Aquasorb; Blanose; Carbose D; carmellosum natricum; Cel-O-Brandt; cellulose gum; Cethylose; CMC sodium; E466; Finnfix; Glykocellan; Nymcel ZSB; SCMC; sodium carboxymethylcellulose; sodium cellulose glycolate; Sunrose; Tylose CB; Tylose MGA; Walocel C; Xylo-Mucine.

3 Chemical Name and CAS Registry Number

Cellulose, carboxymethyl ether, sodium salt [9004-32-4]

4 Empirical Formula and Molecular Weight The USP 32 describes carboxymethylcellulose sodium as the sodium salt of a polycarboxymethyl ether of cellulose.

5 Functional Category

Coating agent; stabilizing agent; suspending agent; tablet and capsule disintegrant; tablet binder; viscosity-increasing agent; water-absorbing agent.

6 Applications in Pharmaceutical Formulation or Technology

Carboxymethylcellulose sodium is widely used in oral and topical pharmaceutical formulations, primarily for its viscosity-increasing properties. Viscous aqueous solutions are used to suspend powders intended for either topical application or oral and parenteral administration. Carboxymethylcellulose sodium may also be used as a tablet binder and disintegrant, and to stabilize emulsions.Higher concentrations, usually 3–6%, of the medium-viscosity grade are used to produce gels that can be used as the base for applications and pastes; glycols are often included in such gels to prevent them drying out. Carboxymethylcellulose sodium is also used in self-adhesive ostomy, wound care, and dermatological patches as a muco-adhesive and to absorb wound exudate or transepidermal water and sweat. This muco-adhesive property is used in products designed to prevent post-surgical tissue adhesions; and to localize and modify the release kinetics of active ingredients applied to mucous membranes; and for bone repair.Encapsulation with carboxymethylcellulose sodium can affect drug protection and delivery. There have also been reports of its use as cyto-protective agent.Carboxymethylcellulose sodium is also used in cosmetics, toiletries, surgical prosthetics, and incontinence, personal hygiene, and food products.

TableI: Uses of carboxymethylcellulose sodium.

Uses	**Concentration (%)**
Emulsifying Agent	0.25-1.0
Gel-forming agent	3-6
Injections	0.05-0.75
Oral solutions	0.1-1.0
Tablet binder	1-6

7 Description

Carboxymethylcellulose sodium occurs as a white to almost white, odorless, tasteless, granular powder. It is hygroscopic after drying.

8 Typical Properties

Density (bulk) 0.52 g/cm3
Density (tapped) 0.78 g/cm3
Dissociation constant pKa = 4.30

Melting point Browns at approximately 227^{o}C, and chars at approximately 252^{o}C.Moisture content, typically contains less than 10% water. However, carboxymethylcellulose sodium is hygroscopic and absorbs significant amounts of water at temperatures up to 37^{o}C at relative humidities of about 80%.

Solubility Practically insoluble in acetone, ethanol (95%), ether, and toluene. Easily dispersed in water at all temperatures,forming clear, colloidal solutions. The aqueous solubility varies with the degree of substitution (DS).

Viscosity Various grades of carboxymethylcellulose sodium are commercially available that have differing aqueous viscosities; Aqueous 1% w/v solutions with viscosities of 5–2000 mPa s (5–2000 cP) may be obtained. An increase in concentration results in an increase in aqueous solution viscosity.Prolonged heating at high temperatures will depolymerize the gum and permanently decrease the viscosity. The viscosity of sodium carboxymethylcellulose solutions is fairly stable over a pH range of 4–10. The optimum pH range is neutral.

9 Stability and Storage Conditions

Carboxymethylcellulose sodium is a stable, though hygroscopic material. Under high-humidity conditions, carboxymethylcellulose sodium can absorb a large quantity (>50%) of water. In tablets, this has been associated with a decrease in tablet hardness and an increase in disintegration time.

Aqueous solutions are stable at pH 2–10; precipitation can occur below pH 2, and solution viscosity decreases rapidly above pH 10. Generally, solutions exhibit maximum

viscosity and stability at pH 7–9. Carboxymethylcellulose sodium may be sterilized in the dry state by maintaining it at a temperature of 160°C for 1 hour. However, this process results in a significant decrease in viscosity and some deterioration in the properties of solutions prepared from the sterilized material.

Aqueous solutions may similarly be sterilized by heating, although this also results in some reduction in viscosity. After autoclaving, viscosity is reduced by about 25%, but this reduction is less marked than for solutions prepared from material sterilized in the dry state. The extent of the reduction is dependent on the molecular weight and degree of substitution; higher molecular weight grades generally undergo a greater percentage reduction in viscosity.Sterilization of solutions by gamma irradiation also results in a reduction in viscosity. Aqueous solutions stored for prolonged periods should contain an antimicrobial preservative.The bulk material should be stored in a well-closed container in a cool, dry place.

11 Incompatibilities

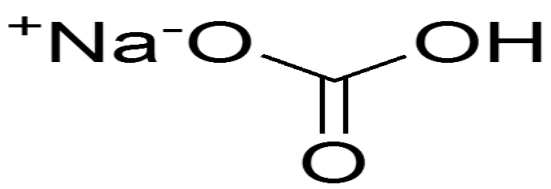
Carboxymethylcellulose sodium is incompatible with strongly acidic solutions and with the soluble salts of iron and some other metals, such as aluminum, mercury, and zinc. It is also incompatible with xanthan gum. Precipitation may occur at pH < 2, and also when it is mixed with ethanol (95%). Carboxymethylcellulose sodium forms complex coacervates with gelatin and pectin. It also forms a complex with collagen and is capable of precipitating certain positively charged proteins.

12 Related Substances

Carboxymethylcellulose calcium.

SODIUM BICARBONATE :

Structure:



- **Non-proprietary Names**
  - **BP:** Sodium bicarbonate.
  - **Ph. Eur.:** Natrii hydrogenocarbonas.
  - **USP:** Sodium bicarbonate.
- **Synonyms:** Baking soda; E500; monosodium carbonate; sodium acid,
- Carbonate: sodium hydrogen carbonate.
- **Chemical Name:** Carbonic acid monosodium salt.
- **Empirical Formula:** $NaHCO_3$
- **Molecular Weight:** 84.01
- **Functional Category:** Alkalizing agent; therapeutic agent.
- **Description:** Sodium bicarbonate occurs as an odorless, white crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms. Grades with different particle sizes, from a fine powder to free flowing uniform granules, are commercially available.
- **Properties:**
- **Density:** 2.159 g/cm3
- **Solubility:** Practically insoluble in Ethanol (95%) and Ether. freely Soluble in water.
- **Stability and Storage condition:** Sodium bicarbonate is stable in dry air but slowly decomposes in moist air should therefore be stored in a well-closed container in a cool, dry, place.
- **Safety:** Sodium bicarbonate is metabolized to the sodium cation, which is eliminating from the body by renal excretion, and the bicarbonate anion, which becomes part of the body's store. Any carbon dioxide is eliminated via the lungs. Administration of excessive amounts of sodium bicarbonate may thus disturb the body's electrolyte balance leading to metabolic alkalosis or possibly sodium overload potentially serious consequences. Orally ingested sodium bicarbonate neutralizes gastric acid with the evolution of carbon dioxide and may cause stomach cramps and flatulence. When used as excipients, sodium bicarbonate is generally regarded as an essentially nontoxic and nonirritant material.

MICROCRYSTALLINE CELLULOSE

Description

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle size Stretching and moisture grades that have different properties and applications.

Formula

$(C_6H_{10}O_5)_n$

Molecular weight:

n~220

Density (bulk):

0.32 g/cm^3

Density (tapped):

0.45g/cm^3

Density (true):

1.512-1.668 g/cm^3

Melting point:

Chars at 260-270 ^{0} C.

Solubility:

Slightly soluble in 5% W/V sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Application in pharmaceutical Formulation Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as binder/diluents in oral tablet and capsule formulations where it is used in both wet granulation and direct-compression process. In addition to its use as a binder /diluents, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Functional Category

Adsorbent; suspending agent; tablet and capsule diluents; tablet disintegrant.

Use of Microcrystalline cellulose

Use	Concentration(%)
Adsorbent	20-90
Antiadherent	5-20
Capsule binder/diluents	20-90
Tablet disintegrant	5-15
Tablet binder/diluents	20-90

Incompatibilities:

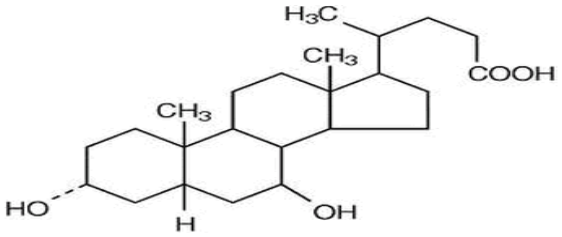
Microcrystalline cellulose is compatible with strong oxidizing agents.

Safety

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a nontoxic and nonirritant material. Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may, however, have a laxative effect, although this is unlikely to be a problem when cellulose is used as excipients in pharmaceutical formulations. Deliberate abuse of formulation containing cellulose, either by inhalation or injection, has resulted in the formulation.

Magnesium Stearate

Chemical structure:



Synonyms: HyQual, magnesium octadecanoate, stearic acid magnesium salt.

Chemical name and CAS registry number: Octadecanoic acid magnesium salt [557-04- 0].

Functional category: Tablet and capsule lubricant.

Applications: It is primarily used as a lubricant in capsule and Tablet manufacture at concentrations between 0.25-5.0percent.

Description: It is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint characteristic odor and taste. The powder is greasy to touch and readily adheres to the skin.

Solubility*:* Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in benzene and warm ethanol (95%).

Stability*:* Magnesium stearate is stable.

Storage conditions: It should be stored in a well-closed container in a cool, dry, place.

Incompatibilities: Incompatible with strong acids, alkalis, iron salts and with strong oxidizing materials.

Safety: It is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may result in some laxative effect or mucosal irritation.

TALC [18]

Synonyms: Magsil Osmanthus, Magsil Star, Purtalc, Steatite.

Chemical Name and CAS Registry Number: Talc [14807-96-6].

Empirical Formula and Molecular Weight*:* Talc is a purified, hydrated, magnesium silicate, approximating to the formula Mg6 (Si2O5)4(OH)4.

Functional category: Glidant, tablet and capsule lubricant, anti- cackling agent.

Applications: It is used as a lubricant in solid dosage forms (1-10%), in topical preparations as dusting powder (90-99 %).

Description: It is a very fine, white to grayish-white colored, odorless, impalpable, unctuous powder. It adheres to the skin, is soft to touch, and free from grittiness

Solubility: Practically insoluble in dilute acids and alkalies, organic solvents and water.

Stability: Talc is a stable material.

Storage conditions: It should be stored in a well-closed container in a cool, dry, place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

Safety: Following oral ingestion talc is not absorbed systemically and may thus be regarded as an essentially nontoxic material.

MATERIALS AND METHODS

Table no: 2

Instrument used

INSTRUMENTS	SUPPLIER/ MANUFACTURER
Single pan analytical balance	Sartorius-Mumbai
Tapped Density Apparatus	Retsec-Mumbai
Disintegration Test Apparatus	Electro Labs-Mumbai
Friabiliator	Electro Labs –Mumbai
Dissolution Test Apparatus	Lab India –Mumbai
UV	Lab India –Mumbai
Mixer/Granulator	Cadmach
FTIR	Schimadzu
Mesh # 21,32	Retsec - Mumbai
Tablet Punching Machine(10 Station)	Karnavati
Hot air oven	Biotechnis India

Table no: 3 Material used

MATERIAL	SUPPLIER/ MANUFACTURER
Quetiapine Fumarate	Micro labs
Lactose	Lobachemie pvt. Ltd
Mannitol	SD fine chemicals
Dicalcium Phosphate	SD fine chemicals
Micro Crystalline Cellouse	Finar chemicals Ltd
Magnesium Stearate	Finar chemicals Ltd
Talc	SD fine chemicals

STANDARD GRAPH FOR ALFUZOSIN

The UV scanning of drug sample was carried out using a solution of drug dissolved in methanol solution at concentration of 100 µg/ ml. The $\lambda_{max\ was}$ observed at 294nm. The calibration curve of Alfuzosin was obtained by dissolving the drug in methanol solutions and absorbance was measured at 244nm in Methanol solution used as blank. Beer's law was obeyed the concentration range of 5-25 µg in methanol solution.

Method of preparation of pH 6.8 Phosphate buffer solution:

224ml of 0.2M NaOH + 500ml of potassium dihydrogen orthophosphate (KH_2PO_4) and makeup the volume to one litres.

How to prepare 0.2M NaOH: Dissolve 8 gm of NaOH in 1000ml of distilled water.

How to prepare KH_2PO_4: Dissolve 27.2 gm of KH_2PO_4 in 1000ml of distilled water.

PROCEDURE:

Accurately weighed quantity of Alfuzosin (100mg) was dissolved in methanol and the volume made up to 100ml with the same.

S.S I ⇒ 1000 mcg/ml.

10ml of Stock solution I was further diluted with 100ml of buffer to get a working standard **S.S I ⇒ 100mcg/ml** Aliquots of 5-25µg of stock solution was pipetted into 10ml volumetric flask and diluted up to the volume with buffer. The absorbance was measured at 294nm against reagent blank (buffer).As shown in the figure and table .Same procedure was employed to extract the standard graph for phosphate buffer 6.8 .As shown in the figure and table.

PREPARATION OF ALFUZOSIN BY PROCEDURE OF DIRECT COMPRESSION

Raw material → weighing → screening → Mixing → Compression

MASTER FORMULATION FOR ALFUZOSIN

Table 5 Master formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Alfuzosin hydrochloride	10	10	10	10	10	10	10	10	10
HPMC K15M	20	30	-	-	20	30	-	-	-
Sodium CMC	-	-	20	30	20	30	-	20	30
Carbopol940	-	-	-	-	-	-	20	20	30
MCC	76	66	76	66	56	46	76	56	46
Sodium Bicarbonate	10	10	10	10	10	10	10	10	10
Magnesium Sterate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2

EVALUATION PARAMETERS

Precompression Parameters

Bulk Density (D_b):

It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

$$D_b = \frac{M}{V_0}$$

Where, M is the mass of powder, V_0 is the bulk volume of the powder

Tapped Density (D_T):

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by

$$D_T = \frac{M}{V_1}$$ Where, M is the mass of powder, V_T is the tapped volume of the powder

Hausner's ratio: Hausner's ratio is the ratio of tapped density to bulk density

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

Angle of Repose:

The frictional forces in a loose powder can be measured by the angle of repose, θ. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane.

Tan θ = $\tan^{-1}$ (h/r)

Where, θ is the angle of repose

H is the height in cms

R is the radius in cms

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height. The angle of repose was then calculated by measuring the height and radius of the heap of powder formed.

Carr's Index (I):

It indicates the ease with which a material can be induced to flow. It is expressed in percentage and is given by

Table Carr's Index limit

Carr's index (%)	**Type of flow**
5 – 15	Excellent
12 – 18	Good
18 – 23	Fair to passable
23 – 35	Poor
35 – 38	Very poor
> 40	Extremely poor

$$\frac{\text{Tapped density- Bulk density}}{\text{Tapped density}} \times 100$$

Post compression Parameters

Hardness:

The hardness of the tablet was determined using a Monsanto hardness tester. It is expressed in **Kg / cm^2.**

Friability (F):

The friability of the tablet was determined using Roche Friabilator. It is expressed in percentage (**%)**. 10 tablets were initially weighed ($W_{initial}$) and transferred into the friabilator. The friabilator was operated at 25 rpm for four mins. The tablets were weighed again (W_{final}). The percentage friability was then calculated.

Weight Variation:

Ten tablets were selected randomly from the lot and weighed individually to check for weight variation. IP limit for weight variation in case of tablets weighing more than 325mg is ± 5%.

Thickness:

The thickness of the tablets was measured by screw gauge. It is expressed in **mm.**

Determination of drug content

10 tablets were randomly selected from the batch, weighed and powdered. Powder equivalent to 100 mg of Alfuzosin was weighed and was diluted with a suitable volume of 0.1M sodium hydroxide to produce a solution containing 0.008% w/v of anhydrous Alfuzosin. The absorbance of the resulting solution was measured spectrophotometrically at the maximum wavelength of about 294 nm, using the solution as a blank which is prepared in the same manner omitting the substance being examined. Calculate the content of Alfuzosin from the absorbance

obtained by repeating the operation using Alfuzosin in place of the substance being examined and from the declared content of Alfuzosin.[14]

***Invitro* dissolution studies:** The *Invitro* dissolution study was carried out in USP dissolution test apparatus type 2 (paddle)

Dissolution Medium: 900ml of simulated gastric fluid

Temperature: 37 ± 0.5 ^{o}C RPM: 50

Volume withdrawn & replaced: 5 ml every 60 minutes. Λmax::244 nm.

STABILITY STUDIES

INTRODUCTION

Stability of a drug can be defined as the time from the date of manufacture and the packaging of the formulation, until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

OBJECTIVE OF THE STABILITY STUDY

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, enabling recommended storage conditions, re-test periods and shelf-lives. Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid this undesirable delay, the principles of accelerated stability studies are adopted. The International Conference on Harmonization (ICH) Guidelines titled "stability testing of New Drug substance and products" (QIA) describes the stability test requirements for drug registration applications in the European Union, Japan and the United States of America. ICH specifies the length of study and storage conditions.

Long-Term Testing: 25^{0}C ± 2^{0}C / 60% RH ± 5% for 12 Months

Accelerated Testing: 40^{0}C ± 2^{0}C / 75% RH ± 5% for 6 Months

Method

The selected formulations were packed in amber-colored bottles, which were tightly plugged with cotton and capped. They were then stored at 40^{0} C / 75% RH for 3months and evaluated for their physical appearance, drug content and drug excipient compatibility at specified intervals of time.

SOME OF THE PROCESSING PROBLEMS AND THERE REMIDIES

Capping: partial or complete separation of top or bottom crowns of tablet main bodey.

Lamination: separation of a tablet into two or more distinct layers.

Table PROCESSING PROBLEMS AND THERE REMIDIES

S.No	Reasons	Remedies
1	Air entrapment in the tablet among granules or among particles.	By pre-compression, Reducing final Compression, Minimizing tableting rate.
2	Deformational properties of formulation during and after compression.	Increasing stress relaxation time
3	Improper/Deep concave punches	Better to use flat punches
4	Over dried granules (Due to lack of cohesion)	By maintaining moisture levels using Hygroscopic materials like MC (Methyl Cellulose), Sorbitol, PEG 4000(Polyethylene glycol) etc.

PICKING AND STICKING

Picking:-

Adherence of the tablet material from the surface of a tablet by a punch

Reasons: Because of engraving or embossing or debossing on the punch tips like Small enclosed areas in the letters like —A", B", D", —O", Q"etc

Remedies: Lettering should be designed as large as possible, even the tablet size Can be increased by reformulation

- Colloidal silica can be added as polishing agent to formula.
- Using additional binder to increase cohesiveness of granules and thereby Causing decreased adherence.
- Plating of punch faces with a chromium material to obtain smooth face Which is non-adherent

Sticking:-

Adherence of tablet material to the die walls resulting in chipping of tablet Edges producing rough edges and causing the lower punches uneasy to move resulting in damage of cam tracks and punch faces.

Reasons: Presence of low melting point substances in the formula ex. stearic acid, PEG (Polyethylene glycol) etc, which gets soften due to compressive heat.

- Excessive moisture in the granules

Remedies: Partial or complete substitution of low melting point components with high melting point materials in the formula.

- Proper drying of the granules to remove excessive moisture.

WEIGHT VARIATION

Granule size and size distribution

Reasons: Proportion of small to large granules influence the die filling capacity and thereby results in weight variation of tablets.

• If large granules are used to fill small die cavities, even a small difference in granules results in high percent weight variation of tablets.

Remedies: Uniform size distribution (Narrow) and small granular size is preferable.

Poor flow

Reasons: Improper design of hopper

• Poor flow of granules

• Bridging/arching and rat-holing of granules at the bottom of the hopper

• Segregation or stratification of parties due to use of flow promotion Devices like vibrators.

• Surges of excessive flow above the hopper

Remedies: Flow can be improved by using glidants like talc, colloidal silica etc.

• By proper design of the hopper

• By using flow enhancing devices like vibrators

• By preparing uniform sized and shaped granules

Poor mixing

Reasons: Improper mixing of ingredients like glidants and lubricants useful for proper flow and punching

• Insufficient or inadequate time of mixing

Remedy Proper mixing by maintaining adequate time and using suitable mixer.

Punch variation

Reason: unequal lengths of lower punches which results in the variation of granular volume filled in the die.

Remedy: proper tooling by using good and uniform sized punches.

Hardness variation

Reason: 1) due to weight variation in granules filled in the die.

2) Space between lower and upper punches.

Remedy: Proper tooling of machine**.**

Double impression

Reason: uncontrolled movement of punches with engravings on them.

Remedy: Using ant turning device.

ANALYTICAL DATA ALFUZOSIN DRUG % RELEASE
DISSOLUTION

***Invitro* dissolution study**

Invitro release studies were carried out by using United States Pharmacopoeia (USP) 23 Dissolution Testing Apparatus II (Paddle method). The dissolution test was performed using 900 ml of 0.1N HCl (pH 1.2) at 37±0.5oC. 50 rpm was maintained, 5 ml of sample was withdrawn at predetermined time intervals for 24 hours and the same volume of the fresh medium was replaced. The absorbance of the withdrawn sample was measured spectrophotometrically at a wavelength of about 294 nm and cumulative percentage drug release was calculated using an equation obtained from a standard curve.[15]

Acid Resistance Stage

Dissolution Medium: 900ml of simulated gastric fluid

Number of baskets : 6 baskets

Medium : 0. 1N Hcl

Type : USP –II

RPM : 50

Volume : 900ml

Run time : 10hr

Temp : 37± 0.5º C.

Apparatus Classification in the USP

Apparatus 1 (rotating basket)

Apparatus 2 (paddle assembly)

Apparatus 3 (reciprocating cylinder)

Apparatus 4 (flow-through cell)

Apparatus 5 (paddle over disk)

Apparatus 6 (cylinder)

Apparatus 7 (reciprocating holder).

In the present experiment apparatus 2 is used.

Apparatus Classification in the European Pharmacopoeia (2002) for Different Dosage Forms	
For Solid dosage forms	Paddle apparatus Basket apparatus Flow-through apparatus
For Transdermal patches	Cell method
For Special dosage forms	Rotating cylinder method Chewing apparatus (medicated Chewing gums), Flow-through apparatus,

Figure Apparatus classification as per European pharmacopoeia

FOURIER TRANSFORM INFRARED SPECTROSCOPY STUDIES

Principle: Electromagnetic radiation ranging between 500cm^{-1} and 4000cm^{-1} is passed through a sample and is absorbed by the bondes of the molecules in the sample causing them to stretch or bend.The wave length of the radiation absorbed is characteristic of the bond absorbing it.[16]

Region	Wavelength(μm)	Wave number(cm^{-1})
Near IR	0.78-2.5	12500-4000
Mid IR	2.5-25.0	4000-400
Far IR	25-200	400-10

Table FTIR absorption peaks

Equipment Details

Manufacture: Shimadzu

Software: spectrum 100.

The mid IR region of analytical importance. FT IR spectroscopy is used to determine the functional groups in the drug molecule. We can elucidate the structure of drugs. Mainly it is used for structural elucidation .Based on the drug given in figure 21 and the optimized formulation given in figure 25 ,comparing the spectrum in both we conclude that the spectrums are correlated with each other.

TABLE FOURIER TRANSFORM INFRARED SPECTROSCOPY

S.No	Peaks	Functional group
1	3668.62 & 3346.30	OH (Alcohol)
2	3051.96	Aromatic C-H Stretching
3	3015.42	Alkene C-H Stretching
4	2950.80 & 2893.72	Alkane C-H Stretching
5	1730.91 & 1709.46	Ketone
6	1621.74	NH (Amine)
7	1396.31, 1372.09, 1351.93 & 1325.98	C-O (Phenol)
8	1081.22, 1159.04, 1182.78	C-N Vibrations
9	600-900	C-H Bending (Aromatic)

Procedure: In the present study,potassium bromide pellet method was employed .The sample are thoroughly mixed with dry powdered potassium bromide .The mixture was compressed to form a disc using dies .The disc was placed in the spectrophotometer and the spectrum was recorded.

Determination of floating parameter

a) *Invitro* buoyancy test

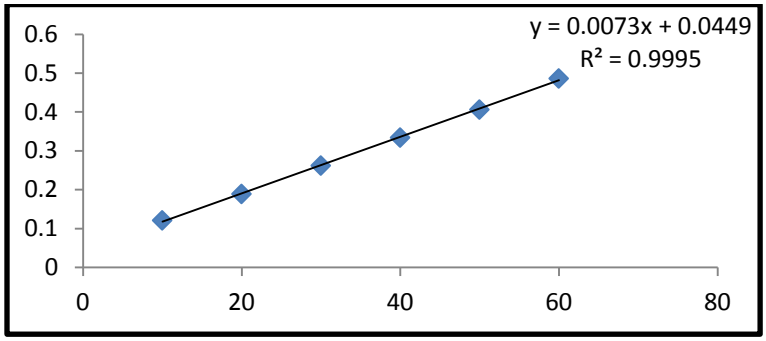
The *invitro* buoyancy was determined by observing floating lag time, as per the method described by Rosa. The tablets were placed in a 100 ml beaker containing 0.1N HCl. The time required for the tablet to rise to the surface and float was considered as the floating lag time.[18]

RESULT AND DISCUSSION

STANDARD GRAPH CALIBRATION CURVE OF ALFUZOSIN

STANDARD GRAPH RESULTS OF 0.1N HCL

Concentration (mcg)	Absorbance at 244nm
10	0.121
20	0.189
30	0.262
40	0.334
50	0.406
60	0.486



20mg in 50 ml further 2.5 in 100ml

5 in 100ml

7.5 in 100ml

10 in 100ml

12.5 in 100ml

15 in 100 ml

ASSAY OF ALFUZOSIN

		AF1	AF2	AF3	AF4	AF5	AF6	AF7	AF8	AF9
Std.wt	20									
std.abs	0.334									
spl.wt		121	122	120	119	120.6	123	122	121	124
spl.abs		0.302	0.308	0.306	0.298	0.304	0.307	0.31	0.308	0.312
std.dil.f	0.002									
spl.dil.f	0.002									
std.purity	99.8									
	%Assay	14.92	15.09	15.24	14.97	15.06	14.92	15.19	15.21	15.04

std-20mg in 50 ml further 10 ml in 100 ml

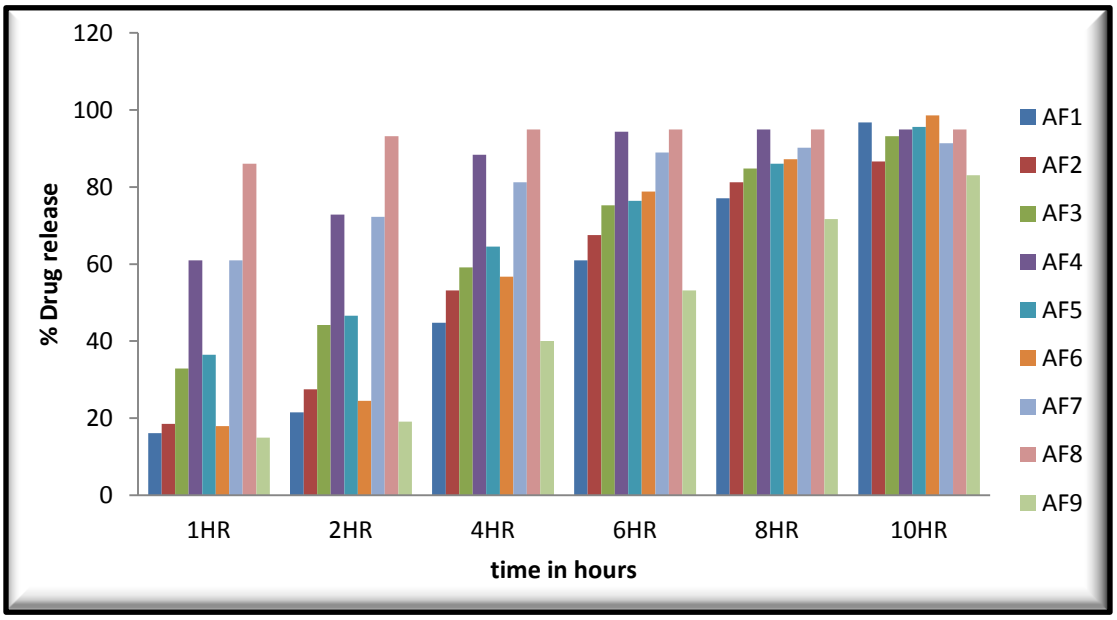
spl-120mg in 50 ml further 10 ml in 100ml

DISSOLUTION STUDIES

Table Dissolution table of formulations in 0.1N HCL

	1HR	2HR	4HR	6HR	8HR	10HR
AF1	16.12	21.5	44.79	60.92	77.05	96.76
AF2	18.51	27.47	53.16	67.49	81.23	86.6
AF3	32.85	44.2	59.13	75.26	84.81	93.17
AF4	60.92	72.87	88.4	94.37	94.97	94.97
AF5	36.43	46.58	64.5	76.45	86.01	95.56
AF6	17.91	24.48	56.74	78.84	87.2	98.55
AF7	60.92	72.27	81.23	88.99	90.19	91.38
AF8	86.01	93.17	94.97	94.97	94.97	94.97
AF9	14.93	19.13	40.01	53.16	71.67	83.02

GRAPHS OF DISSOLUTION STUDIES



PRE AND POST FORMULATION STUDIES

Table Pre-compression parameters of Alfuzosin

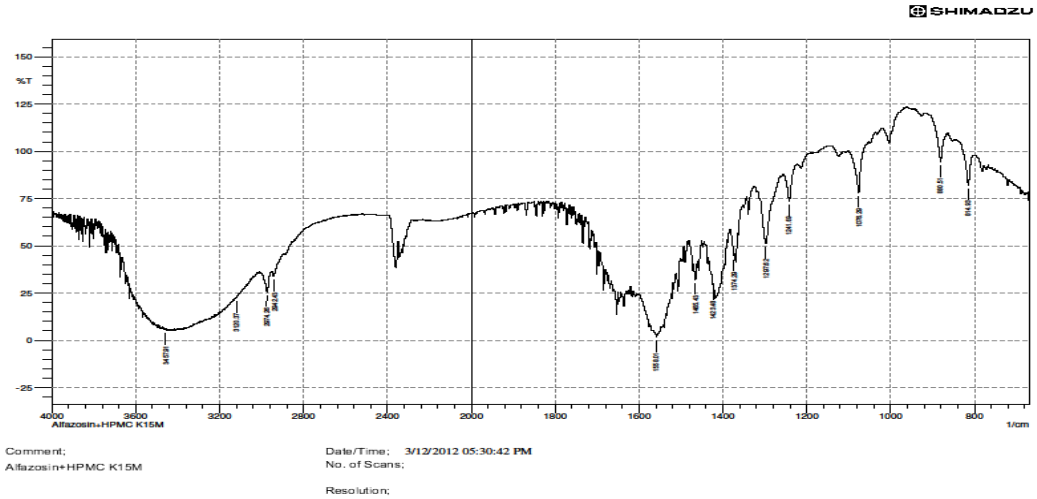
Formulation	Bulk Density(gm\ml)	Tapped Density(gm\ml)	Compressability Index	Hausner's Ratio	Angle Of Repose
F1	0.4	0.476	19	1.19	36.7
F2	0.408	0.50	22.5	1.22	42
F3	0.4	0.512	28	1.28	46
F4	0.416	0.512	23.2	1.23	42.5
F5	0.4	0.487	21.7	1.21	41.7
F6	0.416	0.512	23.27	1.23	43.2
F7	0.411	0.552	25.5	1.34	43
F8	0.41	0.495	24.3	1.20	36
F9	0.413	0.503	22.5	1.21	41

Table Post compression parameters of Alfuzosin

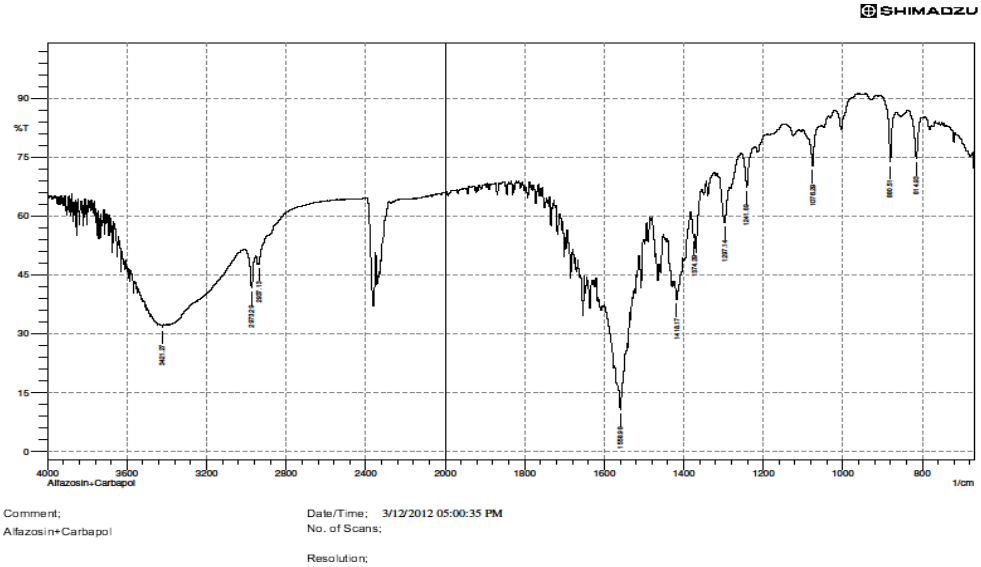
Formulation	Avg.Wt (mg)	Thickness (mm)	Diameter(mm)	Hardness (Kg\cm^2)	Friability	Buoyancy lag Time (sec)	Total floating time (hrs)
F1	121	2.8	7	5.5	0.14	05	<10
F2	120.1	2.6	7	5.4	0.09	04	<12
F3	121.4	2.5	7	5.6	0.12	05	<10
F4	120.6	2.8	7	6	0.07	04	<12
F5	120	2.7	7	5.1	0.2	10	<10
F6	120.1	2.6	7	5.4	0.07	08	<10
F7	120.6	2.6	7	5.5	0.12	08	<10
F8	120.1	2.6	7	5.5	0.14	05	<12
F9	120	2.65	7	5.4	0.09	04	<10

FOURIER TRANSFORM INFRARED SPECTROSCOPY OF ALFUZOSIN

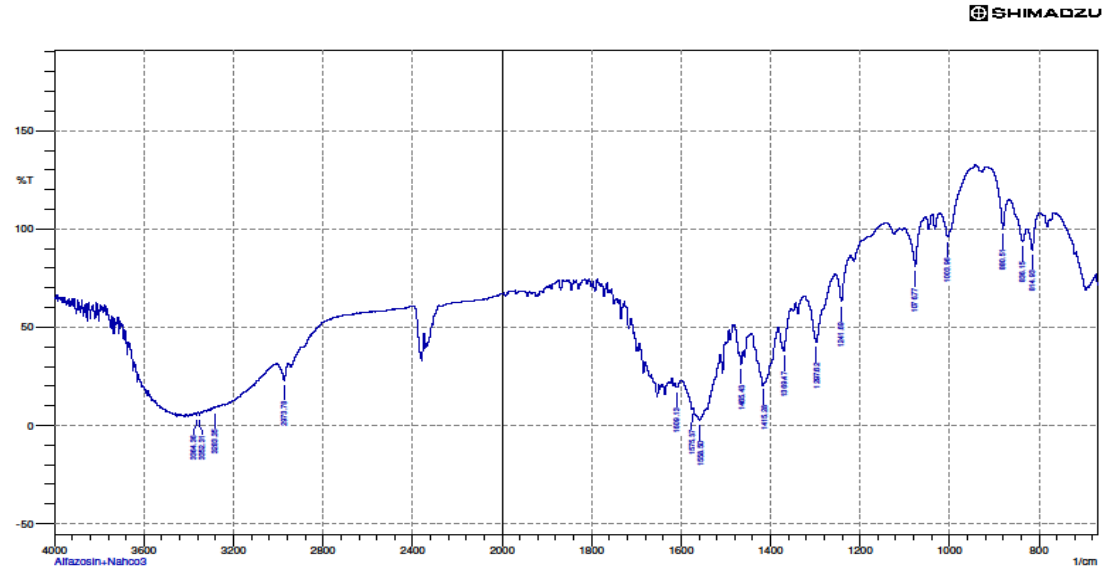
1. Alfuzosin
2. Alfuzosin with HPMC K4M



3. Alfuzosin with Carbopol 940p

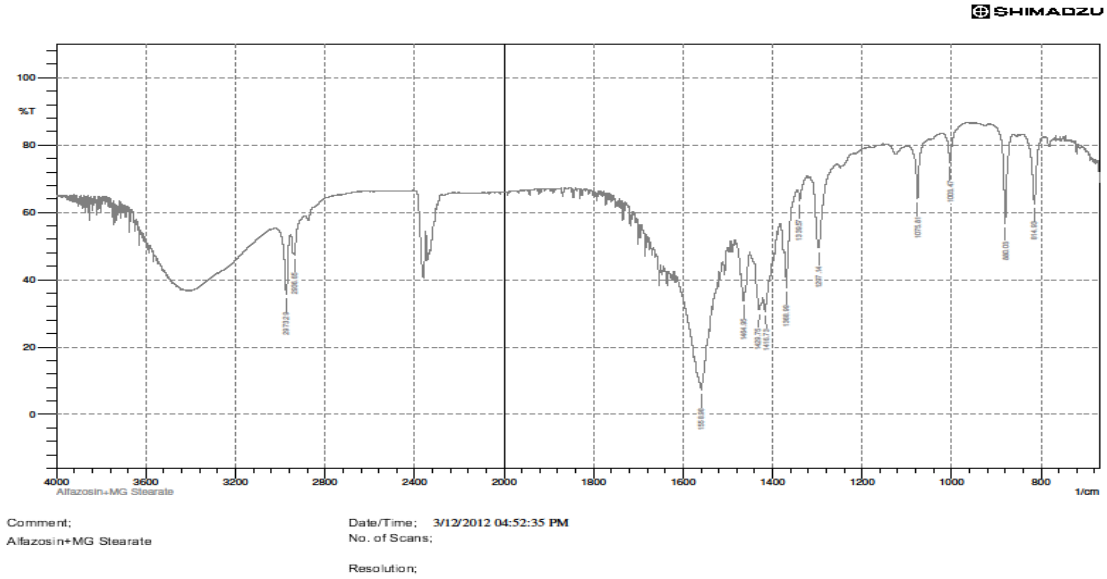


4. Alfuzosin with $NaHCO_3$



5.

5. Alfuzosin with Magnesium Stearate

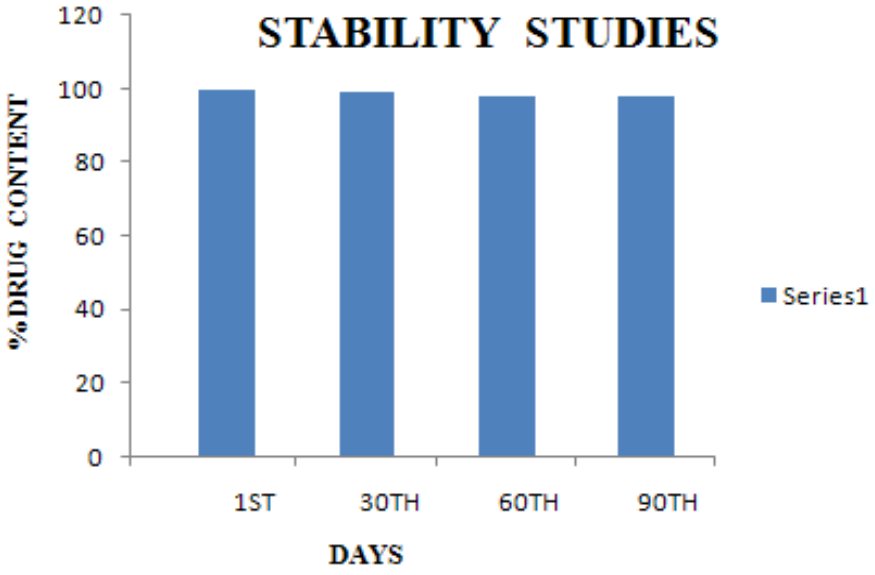


STABILITY STUDIES

Table Stability Data of Formulation 6 at 40 ± 2^0C / 75 ± 5% RH.

Sl. No.	Time in days	Physical changes	Percentage of drug content* ±SD	Moisture content	Percentage of drug release * ±SD (99.5% of release label claim in 10 min).
1.	1st day (initial)	Round, white color uncoated tablets with Concave shape	99.51±0.48	0.82	99.5%
2.	30th day (1 month)	No changes	99.35±0.11	0.78	99.2%
3.	60th day (2 month)	No changes	98.12±0.13	0.80	99.3%
4.	90th day (3 month)	No changes	97.81±0.28	0.78	99.2%

* SD- Standard deviation



GRAPH SHOWING % DRUG CONTENT.

DISCUSSION

In the present study, an attempt has been made to formulate and evaluate floating tablets of Alfuzosin by wet granulation method; employing swellable polymers like Hydroxypropylmethycellulose (HPMC K4M), Carbopol940p, are taken along with other excepients nine formulations are prepared. The formulation is subjected to both pre and post formulation studies.

Hardness and friability: The hardness of the tablet formulations was found to be in the range of 5.1 to 6 kg/cm^2 (Tables-). The friability values were found to be in the range of 0.07 to 0.14 %.(Tables-).

Uniformity of weight: All the prepared tablets of moxifloxacin hydrochloride were evaluated for weight variation. The weight of all the tablets was found to be uniform with low values of standard deviation and within the prescribed IP limits of ±5%.

Uniformity of drug content: The low values of standard deviation indicates uniform drug content within the tablets The percent drug content of all the tablets was found to be in the range of 14.92mg to 15.19mg per tablet (which was within the acceptable limits of ±5%. Tables-)

***In vitro* dissolution study:** *In vitro* dissolution studies were performed in 0.1N HCL on the above promising formulation, namely, formulation 6 .The results are shown in Table- and Table- .

Buoyancy lag Time was observed 04 to 10secnods.
Total floating time (hrs) was observed 10 to 12hours.

FTIR STUDIES.

There is interaction Find in above IR graphs.IR spectra of drug and formulation along with other excipients are shown in figures.

Short-term stability studies Short-term stability studies on the above promising formulations (at 40^{0}C/ 75% RH for 3 months) have shown no significant changes in physical appearance, drug content data of the promising formulation are shown in Tables and figure.

SUMMARY

Pre compression parameters of granules

- It is observed that the results of angle of repose were found to be ranged from 24.69 to 27.7.
- It is observed that the Loose Bulk Density and Tapped Bulk Density were found to be ranged from 0.4 to 0.416 and 0.476 to 0.552 respectively, which are found to be within the prescribed limits.
- The Hausner's ratio of the granules was found to be ranged from 1.19 to 1.34.
- It is observed that the Compressibility index (%) is found to be ranged from 19 to 28.

Post compression parameters of floating tablets:

- It is observed that the tablets prepared in all the formulations were found to be off white, smooth, flat faced circular with no visible cracks.
- The thickness and diameter of tablets were measured by vernier calipers and are found to be ranged from 2.6 mm to 2.8 and 7mm respectively.
- The hardness of the tablets was measured by using Monsanto hardness tester and is found to range from 5.1 to 6 kg/cm^2. The hardness of the tablets in all the formulations is found to be within prescribed limits.
- The friability was measured by using Friabilator and was found to be ranged from 0.09 to 0.14, which is an indication of satisfactory mechanical resistance of tablet.
- The drug content estimation showed values in the range of 14.92mg/tab to 15.19mg/tab which reflects good uniformity in drug content among different formulations variation was found within the IP limit of ±5%.
- The weight variation test was ranged from 120 to 121.4. The percentage weight variation was found within the IP limit of ±5% of the weight.
- All the formulations showed the values within the prescribed limits for tests like hardness, friability, weight variation, drug content which indicate that the prepared tablets are of standard quality.

***Invitro* dissolution studies:**

- *Invitro* dissolution studies of all formulations of floating tablets were carried out in 0.1N HCl. The study was performed for 10hrs and the cumulative drug release was calculated at every 60 min interval.
- The *invitro* drug release for formulations with polymer HPMC K15M (F1 to F9) was ranged from 83.02 to98.55 % for 10hrs
- The maximum *invitro* drug release for formulations with polymer HPMC K15M (F6) was ranged from 98.55% for 10hrs.
- The higher rate and extent drug release was observed from the formulations based on HPMC K4M polymer. Varying the amount of HPMC K4M affect the drug release.
- The drug release from K15M and Carbapol was lesser owing to its high viscosity and less permeability of water.

CONCLUSION

In the present work, floating tablets of Alfuzosin were prepared by Direct Compression method. All the tablets were subjected to weight variation, drug content uniformity, and hardness, and friability, water absorption ratio, wetting time, dissolution, drug excipients interaction and short-term stability studies.

Based on the above study following conclusions can be drawn:

- Tablets prepared by wet granulation method were found to be good without any chipping, capping and sticking.
- The hardness of the prepared tablets was found to be in the range of 5.4 to 6 kg/ cm^2.
- The friability values were found to be in the range of 0.07 to 0.14 %.
- Formulation six showed good results than rest of the nine formulations in pre and post compression studies.
- The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.
- Formulations 6 displayed drug release considered in 0.1N HCL and Formulation 6 shows better drug release in dissolution profile.
- Short-term stability studies of promising formulations indicated that there are no significant changes in drug content.
- IR-spectroscopic studies indicated that there are no drug–excipients interactions.

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